
**REPORT TO
DEPARTMENT OF DEFENSE
ANIMAL CARE AND USE PROGRAMS 2000**

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LIST OF ACRONYMS

AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care International
AALAS	American Association of Laboratory Animal Science
ACLAM	American College of Laboratory Animal Medicine
ACUP	Animal Care and Use Program
ADCS (M&RA)	Assistant Deputy Chief of Staff for Manpower and Reserve Affairs
ADCSPER	Army Assistant Deputy Chief of Staff for Personnel
AFIP	Armed Forces Institute of Pathology
AFRRI	Armed Forces Radiobiology Research Institute
AL/HR	Armstrong Laboratory/Human Resources
APHIS	Animal and Plant Health Inspection Service
ARENA	Applied Research Ethics National Association
ARI	Army Research Institute
ASBREM	Armed Services Biomedical Research Evaluation and Management
ASLAP	American Society of Laboratory Animal Practitioners
AWA	Animal Welfare Act
AWIC	Animal Welfare Information Center
BDCM	bromodichloromethane
BRD	Biomedical Research Database
BUMED	Bureau of Medicine and Surgery
CDR, AFHSD	Commander, Air Force Human Systems Division
CHPPM	Center for Health Promotion & Preventive Medicine
CRISP	Computer Retrieval of Information on Scientific Projects
DARPA	Defense Advanced Research Projects Agency
DDR&E	Director, Defense Research and Engineering
DoD	Department of Defense
DTIC	Defense Technical Information Center
FDA	Food and Drug Administration
FEDRIP	Federal Research in Progress
FY	Fiscal Year
GAO	General Accounting Office
GEIS	Global Emerging Infectious Systems
GME	Graduate Medical Education
IACUC	Institutional Animal Care and Use Committee

ICCVAM	Interagency Coordinating Committee on the Validation of Alternative Methods
IG	Inspector General
ILAR	Institute of Laboratory Animal Research
IRAC	Interagency Research Animal Committee
IRAG	Interagency Regulatory Alternatives Group
JDL	Joint Directors of Laboratories
JTCG	Joint Technology Coordinating Groups
JTWG	Joint Technical Working Group
LAM	Laboratory Animal Medicine
NABR	National Association for Biomedical Research
NAWCTSD	Naval Air Warfare Center Training Systems Division
NHP	Nonhuman Primate
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NPRST	Navy Personnel Research, Studies and Technology
NPY	neuropeptide-Y
NRC	National Research Council
OLAW	Office of Laboratory Animal Welfare
ONR	Office of Naval Research
OSD	Office of the Secretary of Defense
OTSG	Office of the Surgeon General
PHS	Public Health Service
PL	Public Law
POC	Point of Contact (Primary Contact)
RDT&E	Research, Development, Test, and Evaluation
S&T	Science and Technology
SBCCOM	Soldier and Biological Chemical Command
SCAW	Scientists Center for Animal Welfare
SGROC	Surgeon's General Research Oversight Committee
SPF	Standard Protocol Format
STEP	Science and Technology Plan
STRICOM	Simulation Training and Instrumentation Command
STX	Shiga Toxin
TAPSTEM	Training and Personnel Systems Science and Technology Evaluation and Management
USAMRICD	U.S. Army Medical Research Institute of Chemical Defense
USDA	United States Department of Agriculture
USUHS	Uniformed Services University of the Health Sciences
VEE	Venezuelan Equine Encephalitis
WRAIR	Walter Reed Army Institute of Research

SECTION I

INTRODUCTION/OVERVIEW

This is the Fiscal Year (FY) 2000 Report on Department of Defense Animal Care and Use Programs. In addition to a general overview, this report provides a detailed account of Department of Defense (DoD) animal use. It also addresses the DoD's publicly accessible database, animal care and use oversight policies and procedures, alternatives to animal use programs, and the benefits derived from animal use.

I.1 REQUIREMENTS NECESSITATING THE USE OF ANIMALS BY THE DoD

DoD use of animals in research, development, education, and training is critical to sustained technological superiority in military operations in defense of our national interests. The DoD's biomedical research, development, test, and evaluation (RDT&E) and training programs that are dependent upon animal use ultimately translate into improved military readiness as well as reduction in morbidity and mortality associated with military operations. These programs directly contribute to ensuring that service men and women maximize their capabilities to survive the numerous and various hazards they face around the world. The DoD has an irrefutable moral obligation to our soldiers, sailors, airmen, and marines to provide the maximum protection and care possible. Researchers in the DoD are committed to accomplishing this goal, and it is important to emphasize that, as in nonmilitary research programs, the involvement of animals in research cannot be avoided.

DoD research has benefited greatly from animal use alternatives such as nonliving systems, cell and tissue culture, and computer technology. However, complex human organ system interactions, in addition to environmental factors and confounding variables, necessitate the continued judicious use of animal models in DoD programs. Although many innovative animal use alternatives have been developed and are in use by Department scientists, situations remain in which there are no acceptable non-animal alternatives available. For example, there are no adequate models addressing the movement and specific effects of drugs, toxicants, or pathogens in the body. Similarly, cell and tissue cultures are severely limited in their abilities to simulate endocrine, neurological, immune, or inflammatory responses. Whenever possible, the DoD will embrace new advances, technologies, and breakthroughs in animal use alternatives. Section V on alternatives in this report gives a full account of the programs and numerous animal use alternatives implemented in DoD laboratories.

Disease remains a major cause of disability and sometimes death in military operations and conflicts. Today, humanitarian and peacekeeping operations place our troops in regions around the globe, and expose them to endemic pathogens to which their immune systems are naive. Soldier health and performance can be compromised by a variety of diseases for which there are no effective preventive or therapeutic countermeasures. Research toward the development of effective pretreatments and therapies can only be accomplished with the help of specific animal models that support pathogens under study. For example, the life cycles of malaria pathogens require multiple host organ systems, precluding the exclusive use of *in vitro* research studies.

During operations Desert Storm in the Persian Gulf and Restore Hope in Somalia, outbreaks of respiratory diseases, diarrheal diseases such as shigellosis, and parasitic diseases such as leishmaniasis and malaria threatened the health and well-being of our troops. Indeed, the DoD is still assessing and addressing concerns over the long-term effects of various environmental, physical, and medical factors associated with the Persian Gulf Conflict. It is obvious that the health and well-being of military personnel extend far beyond the immediate scope of the battlefield.

One of the most critical areas requiring DoD animal use is the compelling need to develop vaccines, drugs, and therapies to protect, sustain, and treat service men and women during military operations. These therapeutics are needed for protection against numerous militarily relevant diseases and threats, many of which can result in potentially

fatal diseases or conditions that have no known treatments, therapies, or cures. Ethical concerns, as well as regulatory requirements of the Food and Drug Administration (FDA), necessitate that candidate vaccines, drugs, and devices be demonstrated safe and efficacious in laboratory animal models prior to initiation of human use protocols whenever possible. The rationale for this is to prevent the fielding and use of ineffective and unsafe treatments. Drug efficacy screens are generally conducted at the lowest possible phylogenetic level (i.e., in rodents). Given that drug response is often species-specific, promising drugs are subsequently tested in nonhuman primates. During the final stages of vaccine and drug development, large-scale safety and efficacy testing is usually conducted using human volunteers.

The DoD must develop the materiel and technological means to provide critical and immediate battlefield injury care to service men and women. This is often provided by field medical personnel in an austere, harsh, and hostile environment, hours away from full hospital medical care. This contrasts markedly with medical facility counterparts in the civilian community that generally possess well-appointed emergency medicine and trauma management systems. A domestic, low velocity projectile gunshot patient in a modern civilian shock and trauma center will be supported and resuscitated by a full complement of medical staff with a plentiful supply of oxygen, fluids, medications, surgical intervention, and nursing. The combat casualty may be supported by only a single field medic or buddy and the medical supplies, experience, and expertise he or she can carry. No *in vitro* model can simulate the range of effects of multiple organ failure or shock that so often follows physical trauma.

There are numerous research areas, including medical chemical and biological warfare defense, where animal-based studies are particularly critical because human use protocols are simply not possible in the search for understanding and developing protection against many highly lethal agents. Ethical considerations severely restrict or preclude the use of clinical studies in this research area. The world is no longer a place where the deadly chemical poisons and pathogens of mass destruction are controlled by the infrastructure of national governments. The emergence of well-financed terrorist operations such as that associated with the bombing of the Kenyan embassy, as well as the terrorist release of both chemical and biological agents in Japan, underscores the need to develop protective medical countermeasures for both civilian and military personnel. The DoD is charged with the responsibility of identifying and developing these countermeasures to protect the nation, and carefully regulated animal studies are absolutely vital to the success of these biomedical research programs.

This responsibility of the DoD to maintain the health of men and women and their families wherever they work, on bases, on the battlefield, or in peacekeeping missions around the world, underlies the need for the DoD to conduct research, and to train and educate military health care providers. Clinical investigation programs at Medical Treatment Centers support postdoctoral Graduate Medical Education (GME) programs, in which physicians receive residency training in special areas such as pediatrics, orthopedics, surgery, and emergency critical care. To be certified, the GME programs must demonstrate that a medical center has programs to provide research opportunities for both staff and students. These clinical investigation programs provide training in the performance of both laboratory bench and animal research, and the conduct of studies involving human subjects. Not only do these programs provide opportunities for staff and GME students but for patients who desire to participate in research protocols such as the Multicenter Oncology and Pediatric Oncology protocols. In this regard, Congress has mandated that the DoD will work closely with the National Institutes of Health (NIH) to provide more opportunities for DoD beneficiaries to participate in the NIH-sponsored protocols. Many of the clinical investigation training protocols, such as surgical skills training for microvascular or reproductive surgery, support GME programs that follow requirements set by the American College of Surgeons. These courses provide essential opportunities for the training of medical personnel who will work in both military and civilian sectors. Programs using animals for GME training are subjected to veterinarian oversight and are conducted in the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) accredited facilities.

The use of animals is also important in the DoD's nonmedical programs. These studies include the development of biological sensors, sonar, echolocation, biorobotics, aviation construction materials, and hearing and eye protection systems. There are also nonmedical studies to understand learning and memory physiology in an attempt to model the brain's circuitry for advanced data processing computers and robotic machinery. These advanced computers and robots will eventually reduce the risk that our service men and women encounter in their daily duties. The DoD

performs marine biology research to better understand the military working marine mammals. In addition, the marine mammals are investigated to determine their auditory detection thresholds in marine use as sentries. Studies of biosonar systems are conducted to enhance the use of military marine mammal systems for mine detection and retrieval, personnel detection, and reconnaissance.

I.2 DoD Policy Governing Animal Research

The DoD is committed to full ethical and regulatory compliance for its animal-based research programs. It has been proactive in increasing the fixed infrastructure and span of control necessary to ensure lawful and efficient execution of programs and maximize oversight of diverse and varied missions. The Department has aggressively implemented focused programs and working documents that optimize standardization of animal care and use at the user level. This enhanced standardization and oversight have improved a historically good system and made it outstanding.

In 1995, the DoD revised and implemented the directive dealing specifically with animal care and use (DoD Directive 3216.1, “Use of Laboratory Animals in DoD Programs,” 1995) (Appendix A). This directive strengthens and clarifies requirements for nonaffiliated membership in institutional oversight and directs all DoD animal use facilities that maintain animals for RDT&E and training to apply for AAALAC accreditation. DoD veterinarians, researchers, and policymakers continue in their efforts to be proactive in maintaining the highest level of accountability over animal use.

The DoD also implemented a Policy Memorandum entitled “Department of Defense (DoD) Policy for Compliance with Federal Regulations and DoD Directives for the Care and Use of Laboratory Animals in DoD-Sponsored Programs” (Appendix B). This 1995 Policy Memorandum specifies training requirements for nonaffiliated DoD Institutional Animal Care and Use Committee (IACUC) members, implements a standard format for animal use protocols (Appendix C), a standard checklist for IACUC inspections (Appendix D), and a standard reporting requirement for all animal use research to support a publicly accessible database (Section II).

All animal research must conform to requirements of the 1966 Animal Welfare Act (AWA) (Public Law [PL] 89-544) as amended in 1970 (PL 91-579), 1976 (PL 94-279), 1985 (PL 99-198), and 1990 (PL 101-624) as well as the National Research Council’s *Guide for the Care and Use of Laboratory Animals*, (7th rev. edition, 1996), the U.S. Government Principles for Animal Use (1985) (Appendix E), and the requirements of the applicable regulations of the United States Department of Agriculture (USDA).

Mice and rats are the most commonly used species in research. Although the AWA and its implementing regulations currently exempt these species, the DoD has long afforded them, along with all other vertebrates, including fish and frogs, the same consideration given nonexempt species under the AWA. In implementing a full accounting of the use of mice and rats, the DoD is relatively unique in the scientific research community. At the same time, DoD researchers have aggressively developed novel procedures to replace, reduce, and refine the use of animals during research.

I.3 BENEFITS OF ANIMAL RESEARCH

The requirements enumerated in Section I.1 are directed to achieve the benefits derived from DoD animal use research and training that are provided to the active military community. DoD laboratories and extramural contractors provide the capability to solve the medical and nonmedical problems of the future through the efforts of internationally renowned medical and scientific experts working in state-of-the-art facilities and in the field. The Department conducts or funds RDT&E and training to sustain the operational capabilities of today’s service men and women. As noted in the previous section, many of these programs require the use of animals to meet their mission requirements and result in many benefits for both the military and the civilian sector (Tables I-1, I-2, and I-3). The military benefits from programs that do research in areas that currently threaten military personnel, such as combat trauma, chemical and biological agents, infectious diseases not endemic to the United States, directed energy, and occupationally unique

health hazards from military operations and environmental extremes. These research programs contribute significantly to the readiness and sustainment of the DoD's warfighting capability and focus heavily on the prevention of casualties. Further elaboration of military research benefits are noted in Table I-1 and also, provided in a more extensive list of specific benefits found in Appendix F. These benefits reflect the diversity of the DoD research efforts that were extended to military personnel.

It is important to recognize that DoD research requirements benefit civilians in the United States and in the world community. As noted in the previous section, the DoD is charged with the responsibility of developing countermeasures against chemical or biological agents that may be released by terrorists against civilian targets. Both classes of agents were released against Japanese civilians in crowded urban settings in 1995.

The DoD also indirectly or directly advances understanding of our knowledge of cardiovascular disease, trauma care and treatment, respiratory injuries, burns, and specific surgical procedures. The DoD's role in some of these areas is critical in that some of these areas traditionally receive only modest funding support in civilian research programs. Marine researchers and policymakers also benefit from DoD marine mammal research through its indirect contribution of a better understanding of the impact on marine mammals of noise pollution from ships.

With the end of the Cold War, Congress has mandated that the DoD invest some resources in medical research that directly benefits the civilian population such as research in breast, prostate, and ovarian cancer. These model research programs, developed with guidance from the National Academy of Sciences, account for a considerable portion of DoD extramural animal research and are having an immense impact on the understanding, prevention, and treatment of diverse diseases. Transgenic mice, for example, are critical for determining gene effects on the development and progression of cancers. No *in vitro* system exists that can model the extremely complex cellular and molecular "crosstalk" between tissues and cells.

The infectious disease and medical chemical and biological defense research programs are primarily designed to identify potential threats to U.S. military personnel who must operate in a global setting. In FY00, these research programs were awarded patents as shown in Table I-2. While the underlying requirement for disease research is to protect U.S. military men and women, it should be noted that there is an indirect benefit of DoD's research to the broader world community. The scant resources of many equatorial nations are directed at basic survival needs, such as food and medicine, and not research. Because U.S. troops must operate in a worldwide theater, the DoD has had a longstanding commitment to the development of malaria countermeasures. In addition, there are many examples of direct humanitarian benefits of the DoD investment and collaborative efforts with other nations to improve the quality of life of both humans and animals. Several prime examples of the humanitarian benefits of DoD research efforts are noted in Table I-3.

Besides the medical benefits of animal research, there are many nonmedical and training benefits. The development of biosensors and the identification of environmental toxins benefit the military and the civilian communities. The DoD has many exceptional medical and scientific educational programs that train both medical personnel and scientists. While these people are in the military, the DoD reaps the benefit of this training; once they leave the military and apply their training in the private sector, this benefit is realized by the civilian community. The development of alternatives to animal use by the DoD provides an extra value to both communities and to animals as they discover ways to reduce or replace the use of animals. Also, refinement research results in more humane methods of performing research that is applied in many types of research settings.

In FY00, the DoD reported over 432 publications in scientific journals, proceedings, technical reports, books, and book sections from RDT&E efforts using animals. Examples of both journal publications and proceedings by research category are presented in Appendix G.

Table I-1 Animal Use Benefits**Clinical Investigations**

- Clinical research on the development of a HIV vaccine
- Additional insight into mechanism of cellular damage in muscular dystrophy
- Better understanding of the development, diagnosis, and treatment of colon carcinomas
- Identification of induced antibody responses to vaccine development
- Treatment and prevention hemorrhagic shock
- Treatment of acute lung injury
- Treatment of advanced prostate cancer
- Treatments and prevention strategies for neuropsychiatric disorders
- Determine active mechanism affecting altered fluid handling in alcohol exposure
- Research on skin transplants

Medical

- Evaluation of malaria vaccines
- Antigen detection during vaccine development
- Identify mechanism of dermal tissue damage during lesion development
- Determine methodology for inducing controlled hypothermia
- Evaluation of the acute effects of laser exposure
- Research on the mechanisms of human chronic fatigue syndrome
- Quantification of munitions compounds toxicity on wildlife
- Research blast overpressure exposures
- Development of a Decision Tree Network for active topical skin protectants

Nonmedical

- Updating of the national and international laser safety standards
- Identification of environmental and human health risks factors
- Developing toxicity testing
- Developing models to evaluate vascular permeability
- Developing preventative measures for environmental toxins
- Developing arboviral diagnostic assays
- Developing biomonitoring systems
- Evaluating toxicological hazards of chemical threats

Training

- Graduate medical education training
- Students receive psychomotor practice and skill sets
- Advanced medical emergency training
- Advanced trauma life support training
- Veterinary personnel medical emergency training
- Training for research personnel to improve animal-handling techniques and protocol procedure performance

Table I-2 Patents Resulting from Animal Use Research in FY00

Infectious Disease

Induction and detection of antibodies to squalene
Process for making liposomes preparation
Rapid immunoassay for carcinogenic bacteria

Medical Chemical Defense

Buforin and Previns as a specific inhibitor and therapeutic agent for botulinum toxin B and tetanus neurotoxins

Table I-3 Humanitarian Benefits of DoD Research Efforts

In Thailand, Leptospirosis outbreaks have hospitalized thousands and killed hundreds of people in recent years. In FY00, a study was conducted in Sanklaburi District, Kanchanaburi Province to determine if the reservoir for this spirochete is domestic animals or feral rodents that live in close proximity to the human population. This study was a collaborative effort between a U.S. Army laboratory, the Thai Ministry of Agriculture, and Chulalongkorn University.

In Peru, the DoD has investigated epidemiology of viral hemorrhagic and encephalitic diseases among civilians and deployed military troops in Peru. This research has demonstrated that the arthropod-borne viruses most commonly associated with human disease in the Amazon region were Dengue, Oropouche, and Venezuelan Equine Encephalitis (VEE). In addition, Yellow Fever virus, Mayaro, VEE, and one case by an apparently new Phlebovirus (family Bunyaviridae) were isolated from febrile patients in an outbreak in the high jungle near Cusco, Peru. This was the first isolation of Maguari virus, which is associated with human disease.

The DoD performs critical diagnostic analyses of suspected disease outbreaks in the United States and overseas and provides vaccine materials for both humans and animals in emergency settings. DoD research facilities were at the forefront of efforts to diagnose and control outbreaks of: (1) deadly hantavirus infection among Navajo Native Americans in 1993; (2) Rift Valley fever in Egypt in 1993; (3) VEE virus in people and horses in central and South America in 1995; (4) Ebola and related viruses in Zaire in 1995; and (5) West Nile virus in New York citizens, horses, and birds in 1999.

Malaria is one the world's greatest killers, and the DoD's fielding of new drugs is critical in the face of the development of resistance to currently fielded drugs. The Army antimalarial researchers have tested over 500,000 drugs and other substances for activity against malarial pathogens. One new drug developed by the Army, tafenoquin, is highly effective in both malaria prevention and therapy. Should tafenoquin prove safe and efficacious in remaining studies and become licensed by the FDA, it would provide a significant addition to our ability to protect deployed military personnel and civilian populations against malaria.

The DoD collaborated with the Argentine government in the development of a Junin vaccine that has provided critical protection for more than 120,000 individuals in endemic areas of Argentina against the ravages of Argentinean hemorrhagic fever.

I.4 SCOPE OF REPORT

The report covers animal research conducted by the DoD including education, training, and testing both in DoD laboratories and by extramural projects funded by the Department for FY00. This report does not include information on animals used by the DoD solely for the purpose of food preparation for human or animal consumption, ceremonial activities, recreation, or the training, care, and use of military working animals. Information was solicited and received from DoD Military Commands, Agencies, and Activities (hereafter referred to as components) and from non-DoD organizations involved in animal care and use programs located both inside and outside of the United States through the DoD Animal Care and Use Data Collection Web Site. This is an Internet-based system designed to collect and validate data on the DoD animal care and use programs. Through the site, data are entered, edited, validated, and submitted for review and publication, real-time through specially tailored on-line forms that are tied directly to a relational database. The site incorporates multiple layers of security to ensure data entry and retrieval are only performed by those with authorized access. The site typically accommodates over 1,000 offices entering and reviewing data including intramural activities (DoD organizations), and extramural award activities (civilian institutions conducting DoD-funded research). For the purpose of this reporting requirement, an intramural program represents research performed at a DoD facility and funded by either DoD or non-DoD funds. An extramural program represents research performed by a contractor or grantee that is funded by the DoD.

This report provides a comprehensive account of DoD animal care and use programs. There are sections that include in-depth discussions of:

- a. Publicly accessible information on Department research (Section II);
- b. Policies and procedures for oversight of Department animal care and use programs (Section III);
- c. DoD animal use profiles (Section IV); and
- d. DoD initiatives to promote alternative methods that replace, reduce, or refine animal use (Section V).

I.4.1 Publicly Accessible Information on Animal Use in the DoD

On October 1, 1995, the DoD implemented a publicly accessible database analogous to the National Institutes of Health Computer Retrieval of Information on Scientific Projects System. The DoD Biomedical Research Database (BRD) is available on-line to the public, and is composed of succinct summaries of Department research projects, allowing interested individuals easy access to Department research information. It is located at <http://www.dtic.mil/biosys/org/brd/>.

To improve the data collection and reporting procedures and to ensure that the BRD contains accurate, detailed information about individual animal research projects several modifications to the BRD were made in FY00 (Table I-4). Furthermore, in March 2000 the literature search instructions in DoD Standard Protocol Format document were modified to require a search of the BRD (Appendix H).

Table I-4 Modifications to the BRD in FY00

Electronic web-enabled data collection tool Enhanced searching and retrieval system Maintains multiple year records Enhanced help section Additional DoD links Clearer and easier page layout
--

The cost of animal-based research is presented by work unit summary in the BRD. In order to prevent duplication, this information is not presented in this report. More information on accessing the database is presented in Section II.

1.4.2 Oversight of DoD Animal Care and Use Programs

DoD animal use oversight is reviewed in Section III. The stringency of internal and external oversight provisions for DoD animal research is generally as stringent as, and in many cases, more stringent than that at other departments and agencies of the Federal government. The DoD abides by the applicable Federal regulations pertaining to animal care and use, including provisions for oversight. All DoD facilities and extramural institutions sponsored by the DoD must submit protocols for animal use to an IACUC. These communities review proposed animal protocols to ensure compliance with the AWA and its implementing regulations and address concerns of the community. The IACUC must also ensure compliance with DoD Directive 3216.1, which establishes oversight requirements that exceed the provisions of the AWA and its implementing regulations. Each IACUC serves as an independent decision-making body for the institution and establishes policy for the care and use of animals at that facility in accordance with applicable DoD directives and Federal law and regulations.

The DoD has developed and implemented a Standard Protocol Format document/model for use by all of its institutions (Appendix C). In that document, principal investigators must justify the use of animals, their choice of species, and the number of animals to be used. Literature searches must be conducted to provide assurance that the work does not unnecessarily duplicate prior experimentation or ongoing research within the Federal government. All animal use protocols must specify procedures to be used with animals and methods to avoid or minimize pain and distress. A literature search must be conducted for possible animal use alternatives to procedures that may cause more than slight or momentary pain or distress. All “bona fide” alternatives, those that allow the attainment of the goals of the research considered but not employed, must also be enumerated. The qualifications of the individuals conducting the research procedures must be presented, and disposition of animals at the termination of the work must be clearly stated.

The IACUC ensures that personnel involved in animal-based studies are properly trained and, as necessary, establishes programs to train protocol participants. The IACUC inspects facilities and animal care programs at least twice annually, and prepares a written report including a plan to address deficiencies. It enforces compliance with procedures specified in the protocols by conducting inspections, evaluating, and, if necessary, investigating reports of deviation from approved procedures. The DoD 1995 Policy Memorandum (Appendix B) strengthens that process by establishing a standardized semiannual review checklist to consistently cover all program and facility elements. This guidance is consistent with the recommendations of the DoD Inspector General (IG) Report of February 1994 (Appendix I). A formal report of inspection must be prepared twice annually, indicating all major and minor deficiencies, and providing a plan and appropriate schedule for correction of all deficiencies. The document is signed by a majority of IACUC members and includes a statement indicating whether there are or are not minority opinions. In its capacity to serve as an impartial investigator of reports of animal care and use concerns, the IACUC is further empowered to suspend the use of animals for protocols not conducted in accordance with the AWA and its implementing regulations or institutional policy.

DoD Directive 3216.1 clarifies composition, membership, and training requirements of the IACUC. The 1995 modification of the Directive addressed the House Armed Services Committee’s request to improve community representation and to appoint animal advocates to the Department’s IACUCs, consistent with a recommendation of the IG Report of February 1994. In response to the report, the DoD increased the minimum membership of its IACUCs from three to five. In addition, it added a nonscientific member, a member who is not affiliated with the IACUC’s institution, and at least one nonaffiliated alternate member to each IACUC.

This Directive exceeds the requirements of the AWA and its implementing regulations and is further strengthened by the DoD 1995 Policy Memorandum, which requires a minimum of 8 hours of training for new nonaffiliated members. In support of this training, the DoD developed a program consisting of a set of topics and recommended resources that may be used by individual IACUCs.

Per DoD Directive 3216.1, all animal use programs in the DoD are directed to apply for accreditation by the AAALAC. This accreditation is recognized as the “Gold Standard” for animal care and use programs. Currently there are 35 DoD animal programs worldwide, all of which maintained AAALAC accreditation in FY00. During the past 9 years, the DoD has been resolute in pursuing AAALAC accreditation for all of the facilities that use animals in research. This diligence has resulted in an increase in accreditation from 60% in FY93 to 100% in FY00.

While local, institutional oversight rests with each IACUC, DoD-wide oversight responsibility rests with the Director, Defense Research and Engineering (DDR&E), who oversees the Department’s science and technology programs. The preponderance of animal use within the Department occurs in biomedical programs, which receive specific oversight from the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. This committee is chaired by the DDR&E and co-chaired by the Assistant Secretary of Defense for Health Affairs (ASD/HA). The overall biomedical effort is carefully integrated and reviewed to eliminate unjustified duplication of effort by six subordinate Joint Technology Coordinating Groups reporting to the co-chairpersons. To assist it in dealing with matters of animal care and use, the ASBREM Committee is supported by the Joint Technical Working Group for Animal Use, a group largely populated by laboratory animal care veterinarians and that advises on animal care issues across all DoD facilities.

The DoD has funded the Institute of Laboratory Animal Research (ILAR) of the National Research Council to develop institutional training materials, education, and publications in support of DoD laboratory animal care and use programs since 1987. The Department has resolved to maintain this important collaboration by providing in excess of \$130,000 annually for the ILAR Program.

1.4.3 DoD Animal Use Profiles by Research Category

A profile of DoD animal use is provided in Section IV. In this report, a detailed system was adopted for classifying animal use that includes 8 categories with 23 subcategories: 8 medical research, 4 nonmedical research, 3 clinical research, 2 training, and 6 other categories of studies and use. No animals were reported as used for development or testing of offensive weapons. Detailed charts and graphs are included in Section IV.

In FY00, the DoD used 365,803 animals, which is a 12% increase from FY99 and a 34% decrease from FY93. Of the FY00 group, 26,041 (7%) were USDA reportable species as defined in the AWA. This year 187,234 animals were reported used in intramural research programs and 178,569 were used in extramural grants or contracts. Reported intramural animal use decreased by less than 1% (23) in FY00 compared with FY99 use and decreased by 30% (80,857) compared with FY94 use. The intramural programs normally have little variation in the use of animals because they have a continuous mission and ongoing research in specific areas as demonstrated this year. The number of animals reported used in extramural research was 28% (38,729) higher in FY00 than the number in FY99 and 46% (154,023) less than the number used in FY94. Extramural programs by their very nature have large fluctuations in the number of animals used from year-to-year due to a different number of contracts and grants awarded. During the time that the DoD has been collecting animal use data (FY93-FY00), there has been a 34% decrease in the total number of animals used. Table I-5 summarizes the major animal use statistics for DoD research.

Table I-5 Summary of DoD Animal Use Statistics

Total Animal Use by Species	% of Total
Rodents, fish, amphibians, reptiles, and birds	95.95
Rabbits	0.91
Farm Animals (i.e., sheep, pigs, cows, horses, goats, and burros)	1.48
Dogs, cats, nonhuman primates, and marine mammals	0.74
Other	0.93

Percentages may not add up to 100% due to rounding of calculations.

Total Animal Use by Category	% of Use
Medical RDT&E	85.34
Nonmedical RDT&E	4.04
Clinical Investigation	4.53
Adjuncts/Alternatives	4.10
Training and Instructional	1.60
Breeding Stock	0.12
Other	0.38

Percentages may not add up to 100% due to rounding of calculations.

1.4.4 DoD Initiatives to Promote Alternative Methods that Replace, Reduce, and Refine the Use of Animals

Congress requested that Federal departments and agencies establish aggressive programs to replace, reduce, and refine current use of animals. A review of DoD programs and initiatives to develop and implement alternatives to animal research is reviewed in Section V.

Animal research is an essential part of the scientific process, but it is only initiated after due consideration of alternatives. The DoD uses a Standard Protocol Format that specifically requires each investigator to consider alternatives to the use of animals and to justify the animal model selected. The IACUC process includes a strong emphasis on consideration of alternatives in all protocols. All protocols that involve relieved or unrelieved pain or distress require consultation with a veterinarian prior to IACUC review and a database search for scientifically acceptable alternatives to the proposed method. Each protocol that involves animals in research or training must explain the need for the animal research and defend the choice of species as the most scientifically valid model. Often, economies of time and resources are gained when scientifically valid alternatives to animal use are available. Scientists in the DoD have developed or adopted many alternative methods based on ethical considerations and other inherent benefits.

General alternatives are those that are frequently implemented in many different DoD programs. Specific alternatives are those that may be specific to both a research protocol and/or facility. Alternatives presented in Section V are both those developed by DoD investigators and those implemented by the DoD in FY00. Replacement includes the elimination of animal use altogether, generally by adopting *in vitro* or theoretical model study systems. Replacement also includes the substitution of species that are higher on the phylogenetic scale with those that are lower. Reduction is the use of fewer animals without loss of scientific test validity. Refinements include changes in methods that reduce or eliminate animal distress or pain or improve animal quality of life while maintaining or improving the quality/quantity of research data collected.

In FY00, over 700 animal use projects reported that they were implementing alternative methods in animal use. Table I-6 presents examples of alternatives developed by the Department in FY00 to replace, reduce, and refine the use of animals. In addition, the Department sponsors conferences and workshops to promote alternatives to animal research.

Table I-6 Examples of Alternatives for Replacement, Reduction, and Refinement of the Animal Developed or Being Developed by the DoD in FY00

- In the assessment of protection of botulinum neurotoxin fragments against intoxication with botulinum, mice have replaced the use of nonhuman primates.
- In the laser research program, developed cultured human eye cells to evaluate the effects of laser injury and therapeutic approaches.
- Gene and protein expression resulting from laser exposure is being explored in studies on the risk assessment of the eye and safe laser wavelength for cornea and skin.
- Computer models for target detection to replace dolphins are being developed.
- A miniature pig model is being developed to replace the rhesus monkey retinal model used in retinal research.
- Virtual models and robotic trauma manikins that will replace the use of goats in Advanced Trauma Life Support Course Practicum are being developed.
- Procedures and methods for improved environmental enrichment are being developed and evaluated for many research animal species.

I.5 CONCLUSION

It remains essential to use animals in DoD RDT&E or training to protect the health and lives of military personnel. Although animal alternatives will continue to be sought and applied as possible, the complex interactions of organ, tissue, cell, disease agents or processes, and environment make the continued judicious use of animals in DoD programs necessary. Animals are used in research only when scientifically acceptable alternatives are not available. The DoD is committed to full ethical and regulatory compliance for its animal-based research programs. The Department's animal care and use requirements are as strict or stricter than those required of non-DoD, government-funded, or public and private research institutions. The DoD policy directs all facilities maintaining animals for use in RDT&E to apply for AAALAC accreditation, and the DoD has established effective programs to replace, reduce, and refine current use of animals.

SECTION II

PUBLICLY ACCESSIBLE INFORMATION ON ANIMAL USE IN THE DoD

II.1 CREATION OF THE DoD BIOMEDICAL RESEARCH DATABASE

House Armed Services Committee Report 4301 (1995) requested the Secretary of Defense to “develop a mechanism for providing Congress and interested constituents with timely information... about [Department of Defense (DoD)] animal use programs, projects and activities, both intramural and extramural.” In response to this request, and to serve the interest of both the scientific community and general public, the Department has implemented a publicly accessible database called the Department of Defense Biomedical Research Database (BRD). The BRD is a database containing succinct summaries of the Department’s research and training projects involving the use of animals. This database is analogous to the National Institutes of Health (NIH) Computer Retrieval of Information on Scientific Projects (CRISP) System. The CRISP System is a biomedical database containing information on research projects supported by the United States Public Health Service, as well as information on intramural research programs of the NIH and the Food and Drug Administration. The BRD first became accessible to the public through the Internet at <http://www.dtic.mil/biosys/org/brd/> on October 1, 1995.

II.2 MODIFICATIONS TO THE BRD IN FY00

In the 1998 General Accounting Office (GAO) report entitled “DoD Animal Research Improvements Needed in Quality of Biomedical Research Database,” the GAO recommended that the Secretary of Defense continue to take steps to improve the BRD. Specifically, the Secretary should improve the data collection and reporting procedures to ensure that the BRD contains accurate, detailed information about individual animal research projects. In addition, to improve public accountability, they recommend that the Secretary provide other information on the research category for each project and ensure that the information contained in the BRD be presented in a uniform manner for all projects. In March 2000, a search of the BRD became a required literature search in the DoD Standard Protocol Format (Appendix H). To meet these new requirements, several modifications were made to the BRD and the way in which the BRD data are collected.

- Records for the BRD now come directly from the Animal Care and Use Data Collection Web Site database, which is populated with data directly from intramural institutions and extramural researchers in the field during the fiscal year data collection cycle. Summaries are reviewed by their respective responsible organization prior to submission and then again by the publishing authority.
- A thesaurus of keywords was developed to enhance searching and retrieval of summaries and ensure keyword consistency between summaries.
- The BRD search tool has been enhanced by the use of Boolean logic systems and connector fields.
- The Animal Use Research Category Code and description are part of each summary.
- Development of the ability to query BRD records based on Animal Use Research Category Code was incorporated in the search form.
- The BRD now maintains multiple year records (FY98-99) that can be searched. In addition, the summaries from future years will be added to the database.

- The user can select to have a wider range of records returned (50, 100, 250, 500, 1000, and 2000).
- Enhancement of the Help section with step-by-step instructions.
- The BRD homepage provides links to the Deputy Under Secretary of Defense for Science and Technology and BioSystems homepages.
- The BRD has a font that is clearer and easier to read.

II.3 CONTENTS OF THE BRD

Information for the BRD was solicited and received from DoD components involved in animal care and use programs located both in and out of the United States as part of the annual Animal Care and Use data call. These included extramural contractors and grantees that performed animal-based research. The areas of research, development, test and evaluation (RDT&E) in the FY BRD include, but are not limited to, the following: infectious diseases, biological hazards, toxicology, medical chemical and biological defense, military operational medicine, breast cancer research, clinical medicine, clinical surgery, physical protection, training, graduate medical education, and instruction. A work unit summary may refer to a single protocol or a series of protocols that are performed in a given category of animal use. The summaries include the following information:

Title: Title of the work unit.

Research Category: The Animal Use Research Category Code and description as listed in Table IV-1.

Funding by Fiscal Year in Dollars: The funding for the entire work for a given fiscal year. The funding includes civilian salaries, cost of animals, cost of materials, cost of human-based research, cost of non-animal-based research, etc.—all costs related to the work unit except military salaries.

Responsible Organization: The responsible organization is the organization, command, or institution that has responsibility or oversight for the research or training performed. The organization name and the Public Affairs Office contact information are found here.

Performing Organization: The performing organization is the organization the actually performs the RDT&E or training. The organization name and complete mailing address are found here.

Objective and Approach: This section is a narrative on the objectives and the approach of the work unit. This narrative provides a general summary of the work.

Keywords: A list of indexing terms or keywords. The keywords contain “laboratory animals” and the terms for any animal types that may be used in the work unit (e.g., guinea pigs and rats). In addition, they provide descriptors of the research or training project. All keywords are part of a thesaurus developed specifically for the BRD.

The following statement appears at the bottom of each work unit summary. Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to the use of animals in research and was reviewed and approved by the Institute’s Animal Care and Use Committee.

II.4 HOW TO USE THE BRD

The BRD homepage is shown in Figure II-1 and contains a searchable database. It can be accessed at <http://www.dtic.mil/biosys/org/brd/>. To search the BRD select either the “Search the Biomedical Research Database” link at the bottom of the BRD homepage or the “Search” link in the left navigation frame to open the BRD Search Form (Figure II-2). On the Search Form enter search term(s)—word(s) or phrase(s)—in one or any combination of the form’s data entry text fields (Keywords, Title, Responsible Organization, and Performing Organization). The search engine powering this site uses Boolean logic to search for data. The words “AND” and “OR” may be used to separate each word and limit the scope of a search. In addition, you can add negation, wildcard “*” and parentheses to your search term. Here are some examples of search terms that are allowed in any fields:

mouse or mice or rat*
university
(antidote or remedy) and chemical agent*

There is a research category field that contains a drop-down menu with the research categories listed in Table IV-1. The default for this field is “Do not include in search.” To select the fiscal year or years you wish to search, place a check in the appropriate boxes for each fiscal year. You may select as many as you wish. To search across fields, there is a “Field Connector” drop-down menu located at the bottom left of the search page that allows the user to select either “AND” or “OR” to connect all of the search terms entered in the data entry text fields. The default search form “Field Connector” value is “AND,” meaning a search will be conducted for the combination of terms entered in the data entry text fields. Next select the “Max Records Returned” from 50 - 2000 desired for the search from the associated drop-down menu. Finally click the “Submit” button to conduct the search. A linkable list of Work Unit Summary Titles will be returned matching the search terms provided (Figure II-3). To view the information associated with each title, click on the title link and a document will be retrieved containing the appropriate data (Figure II-4).

II.5 UPDATING THE BRD

The DoD made all FY99 work unit summaries of animal use in RDT&E and training available to the public on October 1, 2000. The cost of FY99 animal-based research is presented by work unit summary in the BRD. In order to prevent duplication, this information is not presented in this report. Once the FY00 summary data are ready, they will be loaded into the BRD.

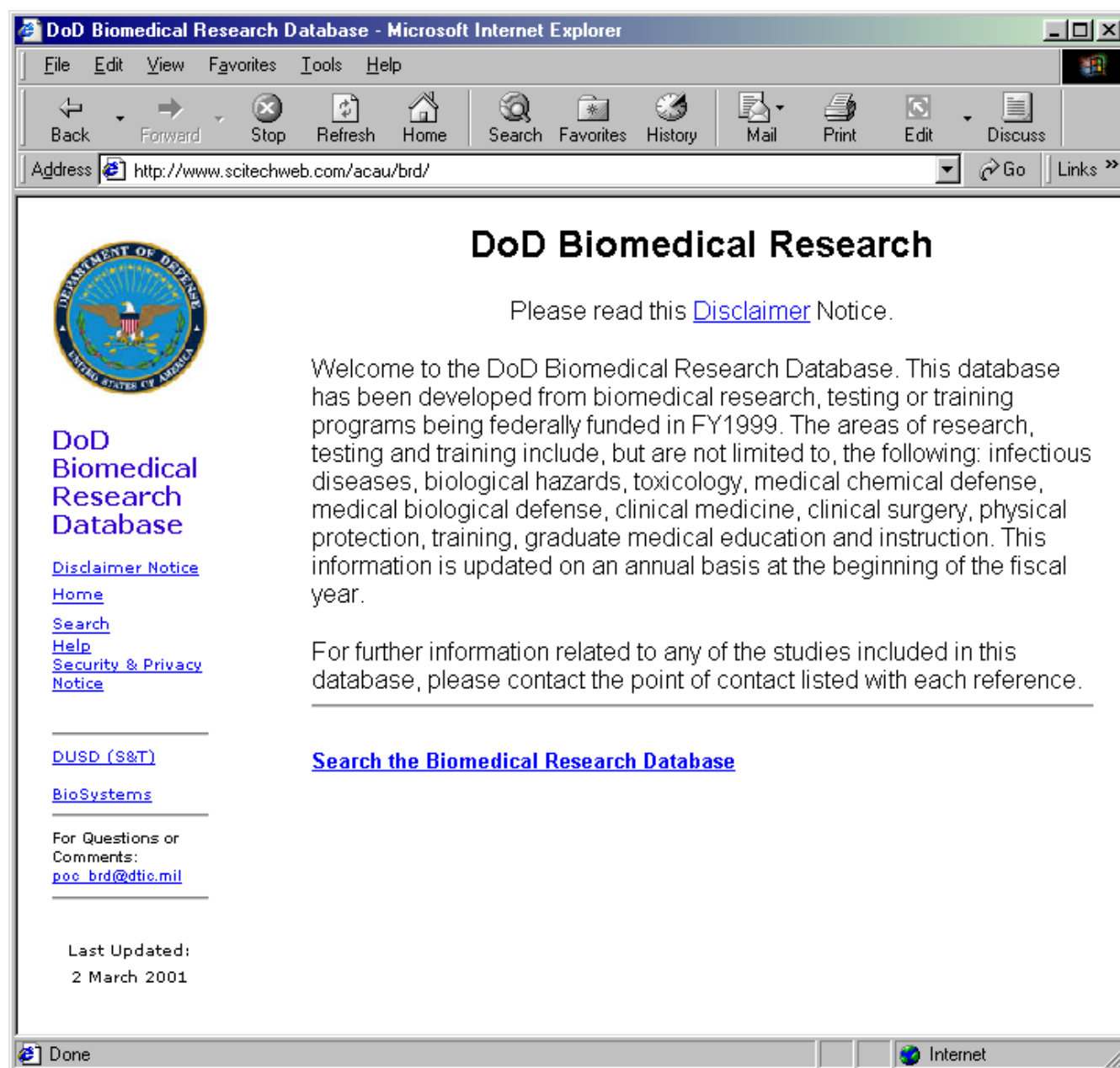



Figure II-1 DoD Biomedical Research Database Homepage

DoD Biomedical Research Database - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Back Forward Stop Refresh Home Search Favorites History Mail Print Edit Discuss

Address <http://www.scitechweb.com/acau/brd/> Go Links >>



DoD Biomedical Research Database

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[Search](#)
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[Security & Privacy Notice](#)

[DUSD \(S&T\)](#)
[BioSystems](#)

For Questions or Comments:
poc_brd@dtic.mil

Last Updated:
2 March 2001

DoD Biomedical Research Database Search Form

Keywords:

Title:

Research Category:

Responsible Organization:

Performing Organization:

Fiscal Year: ☒ FY1998 ☒ FY1999

Max Records Returned:

To search within a field use: "rat and cancer" or "rat or cancer"

To search across fields select:
Example: Search Keywords field and/or Title field

Done Internet

Figure II-2 DoD Biomedical Research Database Search Form

DoD Biomedical Research Database - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Address <http://www.scitechweb.com/acau/brd/> Go Links »



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[BioSystems](#)

For Questions or Comments:
poc_brd@dtic.mil

Last Updated:
2 March 2001

DoD Biomedical Research Database Search Results

23 Documents Retrieved out of 23.
Search Term: ("Keywords: gulf war ")
[\[Return to Query Page\]](#)

Results list Navigation: 1 [2](#) [3](#)

Rank	Document Title
1	Low Level Exposure to GB Vapor in Air: Diagnosis/Dosimetry, Lowest Observable Effect Levels, Performance-Incapacitation, and Possible Delayed Effects
2	LOW LEVEL EXPOSURE TO GB VAPOR IN AIR:DIAGNOSIS/DOSIMETRY, LOWEST OBSERVABLEEFFECT LEVELS, PERFORMANCE-INCAPACITATION, ANDPOSSIBLE DELAYED EFFECTS
3	Long-Term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
4	Sarin and Pyridostigmine Interaction under Physical Stress: Neurotoxic Effects in Mice
5	Effects of Pyridostigmine in Flinders Line Rats Differing in Cholinergic Sensitivity
6	Long-Term Effects of Subchronic Exposure to Sarin, Alone and With Stress or Other Chemicals
7	EFFECTS OF PYRIDOSTIGMINE IN FLINDERS LINE RATSDIFFERING IN CHOLINERGICSENSITIVITY
8	Health Effects of Embedded Depleted Uranium
9	Percutaneous Absorption of Chemical Mixtures Relevant to the Gulf War
10	Toxic Interactions of Prophylactic Drugs and Pesticides

[\[Return to Query Page\]](#)

Internet


Figure II-3 DoD Biomedical Research Database Search Results

DoD Biomedical Research Database - Microsoft Internet Explorer

File Edit View Favorites Tools Help

Address <http://www.scitechweb.com/acau/brd/> Go Links >>

DoD Biomedical Research Database Search Results:



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For Questions or
Comments:
poc_brd@dtic.mil

Last Updated:
2 March 2001

Title:	Long-Term Effects of Subchronic Exposure to Sarin, Alone and with Stress or Other Chemicals
Research Category:	M8: Other Medical RDTE
FY: 1999 Funding (in dollars):	996,000: FY98-FY02
Responsible Organization:	U.S. Army Medical Research and Materiel Command
Primary Contact:	Public Affairs Office
City:	Fort Detrick
State:	MD
Zip:	21702-5012
Performing Organization:	Duke University Medical Center
City:	Durham
State:	NC
Zip:	27710
Keywords:	Laboratory Animals, RA III, Persian Gulf War , lab animal, rat, sarin, pyridostigmine bromide, DEET, permethrin, stress,, blood brain barrier, acetylcholinesterase ,
Objective:	Assess the possible long-term, delayed toxic effects of low-level, subclinical exposure to the nerve agent sarin, alone, or in combination with other factors (stress, heat, pyridostigmine bromide (PB), DEET, and permethrin), which the American soldier may have been exposed to in the Persian Gulf War . The principal investigator (PI) hypothesizes that exposure to low levels of sarin, a potent inhibitor of acetylcholinesterase, may cause neurologic dysfunctions via: (a) downregulation of cholinergic functions due to accumulations of acetylcholine or direct binding of sarin to acetylcholine receptors and/or; (b) increased permeability of the blood brain barrier (BBB) resulting in the possible entrance of xenobiotics, and humoral or immunological factors.
Approach:	The PI proposes the following experiments: (1) dose-finding study for sarin; (2) effect of stress on subclinical sarin exposure; (3) effect of heat on subclinical sarin exposure; (4) effect of PB on subclinical sarin exposure; (5) effect of combined stress and PB on subclinical sarin exposure; (6) effect of combined heat and PB on subclinical sarin exposure; and (7) effect of combined stress, heat, PB, DEET, and permethrin on subclinical sarin exposure. Neurological deficits will be assessed by: (a) clinical condition, (b) neurobehavior, (c) integrity of the BBB, and (d) electrophysiological changes.

Research was conducted in compliance with the Animal Welfare Act and other Federal statutes and regulations relating to the use of animals in research and was reviewed and approved by the Institute's Animal Care and Use Committee.

Internet

Figure II-4 Information Associated with Each Search Title

SECTION III

OVERSIGHT OF DoD ANIMAL CARE AND USE PROGRAMS

This section provides a detailed overview of the formal mechanisms and strategies for providing oversight to the Department's numerous animal care and use programs that support congressionally authorized research, development, test and evaluation (RDT&E) and training. Oversight is governed by Department of Defense (DoD) Directive 3216.1 (Appendix A).

Science and technology (S&T) activities fall under Title II, Research, Development, Test and Evaluation of the Military Departments, for which funds are appropriated within program elements 6.1 (Basic Research), 6.2 (Exploratory Development), and 6.3 (Advanced Development). The vast majority of activities over which the DoD exerts oversight fall under RDT&E and range from basic research to preclinical and clinical studies. Training activities are substantially medical but also include training in animal care and handling. All of these activities receive close and carefully regulated oversight to ensure continuation of the clear and long-standing commitment by the DoD to manage its animal-based research programs in a systematic, comprehensive, and effective manner.

The DoD programs are driven by specific mission requirements and are subjected to a thorough, stratified review and analysis prior to the commitment of funds. Review and evaluation of animal use are fully integrated into this process in accordance with the Animal Welfare Regulations and DoD Directive 3216.1.

At the institutional level, animal care and use oversight is conducted by Institutional Animal Care and Use Committees (IACUCs). Each IACUC is responsible for ensuring that its institution complies with the Animal Welfare Regulations, the DoD Directive 3216.1, and all other applicable laws, regulations, policies, and guidelines. The IACUCs ensure that the DoD uses animals only when necessary to complete its mission and that optimal care is afforded to animals entrusted to their oversight.

DoD mandates well exceed the oversight requirements of the AWA and of many educational, commercial, and governmental institutions. For example, the DoD mandates outside accreditation of its research facilities by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). Additionally, the DoD demands full intramural and extramural accountability for the use of all vertebrates, which embraces birds, rats, mice, frogs, and fish. Full accountability applies to DoD use of animals both in the United States and abroad, and with the further application of any stricter regulations that are present in a host country. All of this ensures accountability, the maintenance of high internationally recognized standards, and consistency in the quality of DoD animal use facilities and programs.

III.1 DETERMINATION OF DoD NEEDS FOR ANIMAL RESEARCH

Determining research needs and plans is a comprehensive process integrated into the DoD's planning, programming, and budgeting mechanisms. Integral elements of these processes are the Department's Research and Development Descriptive Summaries submitted to Congress in justification of the annual budget request. These summaries provide the Office of the Secretary of Defense, the Office of Management and Budget, and Congress with information concerning accomplishments and future plans.

Each DoD research laboratory employs its available resources to tailor its organization, staffing, and related infrastructure to best meet its S&T mission and to support the accountability, responsibility, and authority of its commander. In October 1995, the Department implemented a comprehensive DoD Standard Protocol Format (SPF) as a basis to justify and document all proposed animal use (Appendix C). The SPF solicits specific information that

ensures a thorough review of all animal use proposals by IACUCs. Although there are minor differences in specific procedural elements in protocol review procedures among DoD facilities, the DoD regulations ensure that the overall review mechanisms remain fundamentally similar. The general submission, review, and approval processes are summarized here.

An investigator develops a research protocol in support of departmental S&T guidance and other supplementing instructions developed within the chain of command, both external and internal to the laboratory. Augmenting the formal S&T coordination and review process is a literature search to verify nonduplication of previous or ongoing research. The SPF requires that multiple database searches of ongoing and completed Federal research be performed. The Biomedical Research Database (BRD) and either the Federal Research in Progress or the Computer Retrieval of Information on Scientific Projects (CRISP) databases must be searched. Review and certification that this requirement has been met are integral elements of the review and approval process prior to initiation of a research project.

If animal use is planned for the intended research, the principal investigator must prepare an animal protocol request for submission to the facility IACUC. In addition to the searches for nonduplication of effort, the SPF requires detailed information regarding results and dates of other on-line database searches that may yield alternatives to painful procedures. Databases and resources may include those of the Animal Welfare Information Center, the National Agriculture Library (“AGRICultural OnLine Access” or AGRICOLA), the Johns Hopkins Center for Alternatives to Animal Testing, or the National Library of Medicine (MEDLINE/PubMed). Additional pertinent knowledge and information on the proposed study are gained through review of the scientific literature and participation in scientific meetings, symposia, and workshops detailing other ongoing or completed research.

All individual protocols employing DoD resources are reviewed for factors such as military relevance, necessity, scientific merit, and relative research priority. These reviews are normally conducted within the laboratory’s command-and-control structure and are characterized by features of peer review systems.

III.2 OVERSIGHT OF ANIMAL CARE AND USE PROGRAMS AND FACILITIES

There are three principal vehicles for oversight of animal care and use programs at DoD research facilities: DoD component oversight offices, the local IACUC, and the AAALAC.

III.2.1 DoD Components

III.2.1.1 Military Departments

Each Military Department has one or more organizational elements responsible for oversight and review of its research facilities and animal care and use programs. Periodic reviews, site visits, and inspections are conducted formally and reports are prepared as required.

The Army’s ultimate oversight responsibility rests with the U.S. Army Medical Command. Within this command, oversight is divided between the U.S. Army Medical Research and Materiel Command and the Army Medical Department Center and School. In both subordinate commands, programmatic guidance and oversight are performed by American College of Laboratory Animal Medicine (ACLAM) certified veterinarians with extensive training and experience in laboratory animal medicine (LAM).

The Navy program is administered by two offices: (1) the Office of Naval Research (ONR) within the Office of the Chief of Naval Operations and (2) MED 26 (Research and Development) within MED 02 (Operational Medicine and Fleet Support). Regulatory guidance and oversight are provided by an ACLAM board-certified veterinarian with

extensive training and experience in LAM. This veterinarian also provides support regarding animal care and use issues in biomedical research to the Marine Corps, the Naval School of Health Sciences, the Space and Naval Warfare Systems Command, and the U.S. Navy Bureau of Medicine and Surgery (BUMED) Inspector General (IG). Within ONR, Project Officers and the BUMED veterinarian evaluate all extramural protocols to ensure the scientific validity of the study approach and regulatory compliance. Project funding to these protocols can be withheld if problems are revealed subsequently during administrative reviews or site visits.

U.S. Air Force responsibility for laboratory animal care and use is provided by the U.S. Air Force Office of the Surgeon General in addition to the Commanders of the Air Force Research Laboratory, medical centers, and the Air Force Academy. The U.S. Air Force Surgeon's General Research Oversight Committee (SGROC) monitors all animal use protocols, including those performed at Air Force facilities and those contracted to civilian institutions. The SGROC approves all proposed research prior to initiation for projects involving nonhuman primates, companion animals, and marine mammals. An ACLAM board-certified LAM veterinarian is assigned to the Air Force Surgeon's General Office to monitor the animal use research program and serves on the SGROC.

III.2.2 IACUCs

DoD IACUCs carefully review research proposals involving the care and use of animals for numerous factors including, but not limited to, ensuring that: (a) the study is based on sound scientific principles; (b) a minimum number of animals is used to achieve the stated goals; (c) the lowest phylogenetic species is selected as the appropriate model; (d) there is appropriate use of analgesics and anesthetics or, if required, there is adequate scientific justification for not using anesthetics and analgesics; (e) the research is not duplicative; (f) the research personnel have the training and experience needed to conduct the research; and (g) the scientific question is of sufficient importance to warrant the use of animals. Additionally, IACUCs are required to address detailed information on research elements such as methodology, techniques, and schedules, greatly facilitating a comprehensive and thorough review by IACUCs.

The IACUC proposal or protocol review is the backbone of the institutional review process for all DoD animal-based research. The DoD Directive 3216.1 entitled "Use of Laboratory Animals in DoD Programs" (Appendix A) requires all DoD facilities using animals in research to comply with the Animal Welfare Regulations. These regulations require the Chief Executive Officer (the commander) to appoint an IACUC, qualified through the experience and expertise of its members, to assess the research institution's animal program, facilities, and procedures. Animal Welfare Regulations require that IACUCs have a minimum of three members: an appropriately qualified chairman, at least one member not affiliated with the institution in any way other than as a member of the Committee, and a veterinarian with training or experience in LAM and science. The DoD Directive 3216.1 clarifies the composition, membership, and training requirements of the IACUC and adds additional requirements over those demanded by the AWA and its implementing regulations. The Directive further increases the minimum size of all DoD IACUCs from three to five, which is in concert with the National Institutes of Health (NIH) model. Each DoD IACUC is chaired by an individual with credentials and experience appropriate to the post, typically a senior physician, scientist, or veterinarian. In addition, it specifies that there shall be: (1) at least one nonscientific member on the IACUC, and (2) there shall be at least one member "representing the general community interest who is nonaffiliated with the research facility." The nonaffiliated member and the nonscientific membership can be filled by the same person. To ensure community representation at each meeting and inspection, the Directive also requires an alternate to the nonaffiliated member for all IACUCs having a single nonaffiliated member.

As in FY99, the 35 IACUC panels reporting animal use averaged 9 members each for FY00. Private civilian, government civilian, and military representation on the panels was 7%, 42%, and 51%, respectively.

The diverse backgrounds/professions of the voting (non-alternate) IACUC members are provided in Figure III-1. Occupations/vocations for the alternate IACUC members are presented in Appendix J. Currently, 19% of the voting members are not affiliated with the institutions of their IACUCs. Of these 7% are private sector civilians; the remainder are Federal government civilians or military personnel. In accordance with DoD Directive 3216.1, these members represent the community and are not affiliated with the research facility.

This Directive is further strengthened by the DoD 1995 Policy Memorandum (Appendix B) that directs a minimum of 8 hours of training for the new nonaffiliated members. An average of 12.4 total hours of training was reported for nonaffiliated IACUC panel members in FY00 (Appendix K).

Each IACUC has at least one Doctor of Veterinary Medicine with training or experience in laboratory animal science and medicine who serves as an animal advocate. The U.S. Army Veterinary Corps' formal postgraduate training program in LAM provides didactic training in IACUC composition, function, and regulatory requirements. This training also prepares them to serve as animal advocates. The 35 DoD institutions reporting in FY00 reported an average of two veterinarians serving on their IACUC panels; 21 IACUC panels had two or more veterinarians.

It is a proactive Department policy that nonaffiliated members participate fully in discussions. They are also encouraged to perform unannounced site visits of animal care facilities. In FY00, nonaffiliated members made 33 unannounced visits to Department animal facilities.

The IACUC has statutory responsibility for reviewing the facility's animal care and use program and inspecting the animal facilities on a semiannual basis. Consequently, at least once every 6 months, each IACUC performs an in-depth review of the animal care and use program and inspects the animal facilities. To facilitate these inspections, the DoD has developed and implemented a standardized semiannual program review checklist that details the requirements of the review (Appendix D). All DoD IACUCs use this checklist for their semiannual program reviews. The IACUCs prepare written reports of their evaluations and submit them to the Institutional Official, usually the facility commander. Reports specifically address compliance with the Animal Welfare Regulations, identify any departures from the regulations, and include an explanation for the departure. The report must distinguish between major and minor deficiencies and provide a schedule for the resolution of deficiencies. The IACUCs make recommendations to the Institutional Official regarding the research facility's physical infrastructure, its animal program, or the training of its personnel.

All DoD IACUCs document their meetings and activities, including the results of inspections, complaints, actions, and training. They are empowered to review and investigate concerns involving the care and use of animals at the research facility resulting from complaints received from the public, in-house workers, or reports of noncompliance received from laboratory personnel. To facilitate the reporting and resolution of complaints or concerns, facilities commonly place signs or notices in high-traffic areas and in animal study areas advising both the public and personnel who work with animals how to contact members of the IACUC, facility commanders, and/or the IG whenever questions arise concerning humane care and treatment of animals. The IACUCs review and approve, require modification to, or withhold approval of research protocols involving the use of animals, and suspend an activity involving animals when they determine that the activity is not being conducted in accordance with its approved protocol. DoD facilities have developed a wide variety of proactive and innovative mechanisms to inform the public how to contact responsible individuals and to ensure that those who work with animals are fully apprised of the requirement to provide humane and ethical care.

IACUC Membership by Occupation 309 Voting IACUC Members

Professions	%
Research Scientists	30%
Veterinarians	24%
Other Nonscientists*	17%
Physicians	13%
Animal Technicians	5%
Statisticians	3%
Other Medical**	6%
Clergy/Ethicists	2%

* Other nonscientist occupations are listed in Appendix J

**Nurses, Dentists, Lab Technicians, Pharmacists

Percentages may not add up to 100% due to rounding of calculations

Figure III-1 309 Voting IACUC Members by Occupation

Among the reporting DoD institutions, two complaints were registered during FY00. One report of a possible animal use protocol violation was made jointly by the institute caretaker, technician, and facility manager to the attending veterinarian in December 1999. The facility IACUC conducted an investigation, determined that the violation did occur, suspended the investigator's animal use privileges, and reported the incident through the appropriate chain of command. The investigator was placed in a training program established by the IACUC. Following the successful completion of the training program, the investigator's animal use privileges were reinstated in August 2000 clearly illustrating the oversight process. At a second institution, an anonymous complaint was submitted to the IACUC regarding a protocol that appeared to cause discomfort in laboratory rabbits. The IACUC worked with the investigator to refine the protocol by instituting earlier termination of the experimental period so as to avoid unnecessary discomfort.

III.2.3 AAALAC

The AAALAC is a nonprofit organization chartered to promote high quality standards of animal care, use, and welfare through the accreditation process. The AAALAC accreditation process provides scientists and administrators with an independent, rigorous assessment of an organization's animal care and use program.

The DoD recognizes the benefits of accreditation by the AAALAC and is committed to continuing its full participation in the AAALAC accreditation process in order to effect external peer review for assessing program compliance with regulations, guidance, and ethical responsibility. The DoD Directive 3216.1 requires that all DoD laboratories maintaining animals for use in RDT&E or training apply for AAALAC accreditation.

With the publication of the Joint Regulation on the Use of Animals in DoD Programs, June 1, 1984, the DoD implemented more stringent animal care and use requirements than those required by statute. The Joint Regulation establishes uniform procedures, policies, and responsibilities for the use of animals in the DoD.

The Joint Regulation also cites the National Research Council (NRC) publication, *Guide for the Care and Use of Laboratory Animals*, which is the principal document used by the AAALAC in its accreditation process. The animal care and husbandry standards and requirements contained in the Guide are designed to provide an environment that ensures proper care and humane treatment are given to all animals used in RDT&E and training. This care requires scientific and professional judgment based on knowledge of the husbandry needs of each species, as well as the special requirements of the research program.

III.2.3.1 AAALAC Accreditation

AAALAC accreditation is widely accepted by the scientific community and viewed as an extremely desirable feature of the Department's animal care and use programs. The Association is highly respected as an independent organization that evaluates the quality of laboratory animal care and use both in the United States and overseas. Accreditation covers all aspects of animal care including institutional policies, laboratory animal husbandry, veterinary care, facility physical plant, support facilities, and special areas of breeding colony operations and animal research involving hazardous agents such as radioactive substances, infectious agents, or toxic chemicals.

The independent and external peer review that is fundamental to continuing AAALAC accreditation is valuable to any program. Regular, periodic AAALAC site visits highlight program strengths and identify potential weaknesses, and laboratories maintaining accreditation demonstrate a high degree of accountability and program excellence. AAALAC standards also stress the appropriate appointment, composition, and empowerment of IACUCs.

III.2.3.2 AAALAC Accreditation Status for DoD Programs

The number of DoD AAALAC institutions that maintain animals for research, education, testing, and/or training has significantly increased over the past 8 years (Figure III-2). Worldwide, all 35 DoD institutions with animal-holding facilities reporting animal use in FY00 are AAALAC accredited. Four small detachments assigned to DoD bases share animal use facilities but maintain their own animal care and use programs. Appendix L provides additional information on AAALAC accreditation by program.

There are four DoD research laboratories and one medical center outside the United States using animals. In foreign countries, issues of sovereignty often complicate the accreditation process; local governments have their own regulations and policies that must be considered. Renegotiation of various agreements may be involved in construction or renovation projects. Despite these and various other impediments, the DoD has raised the standard of excellence in its animal care and use programs and facilities by receiving full accreditation for all four of its overseas research laboratories. The Naval Medical Research Center Detachment in Lima, Peru; the Naval Medical Research Unit #2 in Jakarta, Indonesia; and the Naval Medical Research Unit #3 in Cairo, Egypt were the first laboratories to be AAALAC accredited in South America, Southeast Asia, and Africa, respectively. The animal facility of the Armed Forces Research Institute of Medical Sciences in Bangkok, Thailand completed a 50-million dollar renovation and was accredited in 1999.

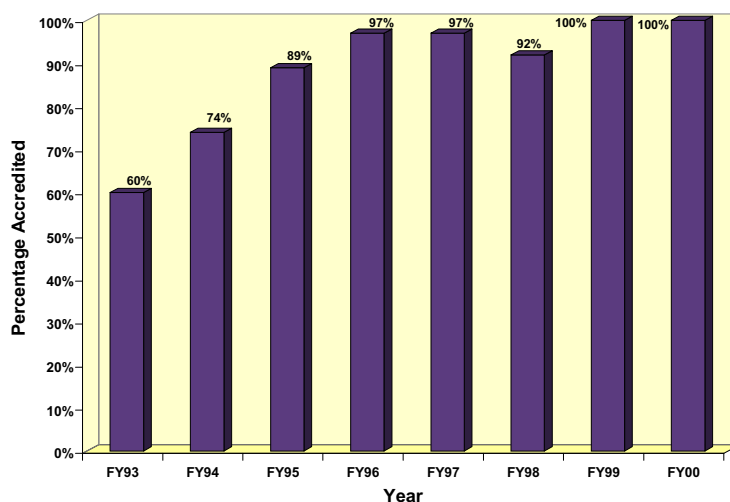


Figure III-2 DoD AAALAC Accreditation FY93 to FY00

III.2.4 DoD Program Reviews

The DoD utilizes external peer review by the Joint Commission for Accreditation of Health Organizations to evaluate many of its programs such as drug-screening laboratories and military medical facilities. At the same time, the DoD recognizes the diversity of mission operations and the global reach of the military mission. There are situations where external peer reviews are not cost effective due to remote locale, limited scope of operations, or host nation sovereignty. In these cases, equivalency standards can be applied and effectively monitored. The Joint Regulation and Service-conducted inspections of facilities implement the requirements of the AWA and its implementing regulations and the 1996 NRC *Guide for the Care and Use of Laboratory Animals*.

As part of the Cooperative Threat Reduction Program, the DoD is involved in a collaborative effort with the Department of State and the government of Russia to sponsor animal research at several Russian institutes. In this capacity, DoD laboratory animal veterinarians conducted site visits at the Russian institutes and determined that the institutes did not meet DoD standards for research involving animals. The DoD laboratory animal veterinarians made recommendations on facility and program improvements necessary to meet the standards. The DoD halted U.S. research funding to these institutions until DoD laboratory animal veterinarians establish that the animal facilities and programs are upgraded to meet modern standards with appropriate oversight to start animal research.

III.2.5 Training

The DoD provides extensive veterinary and animal care services at its facilities and depends on veterinarians with specialty training in LAM. They serve as a valuable resource to the research staff and the IACUC to ensure that all research methods and maintenance procedures are consistent with the latest principles of animal medicine and the current interpretations and implementing regulations of the AWA. The DoD sponsors formal postdoctoral training programs for veterinarians in LAM, including a nationally recognized, in-house 4-year program consisting of 2 years

of residency training and 2 years of practical experience, culminating in specialty board eligibility for certification by the ACLAM. In August 1995, the DoD began a formal postgraduate Master's of Public Health in Laboratory Animal Medicine at the Uniformed Services University of the Health Sciences (USUHS). This outstanding program provides the Department with a new source of LAM experts who will significantly enhance animal welfare in our research laboratories. The DoD veterinarians completing the USUHS postgraduate LAM training program also go on to complete 2 years of practical experience. It is significant that approximately 28% of the current membership of ACLAM, the veterinary specialty most closely associated with animal welfare and laboratory animal care and use, received either all or part of their training in DoD-sponsored LAM training programs.

In addition to veterinarians, the DoD trains Animal Care Specialists (Military Occupation Specialty 91T) to assist in the daily management, care, and treatment of laboratory animals. Over the last 32 years, the DoD has trained over 4,900 Animal Care Specialists. Since 1986, the Division of Veterinary Medicine, Walter Reed Army Institute of Research (WRAIR) has continued to sponsor the DoD Laboratory Animal Workshop program. Some workshops taught there focus on species-specific techniques and handling while others provide general laboratory animal information required by Federal law and other guidelines for the research mission. Successful completion of the workshops fulfills the training requirements for researchers using animals in study protocols. In FY00, the DoD Laboratory Animal Workshops at the WRAIR trained 176 investigators (21%) and 453 technicians (79%), totaling 629 students, a number doubling that of FY99. The schedule of courses is provided in Appendix M. Additionally, DoD research institutions send appropriate staff to a variety of seminars and workshops sponsored by the NIH, other Federal agencies, and private institutions dedicated to the proper care and use of research animals. The Annual Public Responsibility in Medicine and Research Meeting is an outstanding example of this type of training.

The DoD provides detailed informational and instructional material to all members of the IACUC, including nonaffiliated members, to ensure that they are fully cognizant of the numerous responsibilities of IACUC members under the provisions of the AWA and its implementing regulations. The DoD Directive 3216.1 requires new nonaffiliated IACUC members to receive an initial 8 hours of training and continued training for IACUC members, investigators, and technicians.

Formal training on animal care and use issues is provided to all appropriate personnel in Department research laboratories in accordance with the provisions of the AWA and its implementing regulations. Examples of training or materials currently provided to IACUC members are detailed in Appendix K. Hours of training for affiliated and nonaffiliated IACUC members were 11.6 and 12.4, respectively, in FY00. Training resources vary greatly and range from traditional instructional aids such as paper and audiovisual resources, to presentations and courses conducted by veterinarians and attendance at conferences addressing protocol evaluation and laboratory animal care and use. Regular IACUC meeting presentations and distribution of journals such as *Lab Animal* are commonly conducted. Appendix K lists topics that range from animal care and handling to the role of the IACUC and the reporting of suspected violations of animal rights.

One of the examples listed in Appendix K is the Institute of Laboratory Animal Research publication, *A Guide for Care and Use of Laboratory Animals*. As one of the major sponsors of this publication, the DoD has established a formal relationship with the NRC, an extension of the National Academy of Sciences. The publication is used as a guide by the DoD and has been translated into several languages. Many countries use this publication to train and educate personnel.

Although training is an individual institute's responsibility, the DoD has developed a program consisting of a set of topics and recommended resources to support the training requirement (Appendix K). The topics are meant to be general and allow for tailoring of the training to meet an institute's specific needs. The recommended resources are readily available. Efforts are also under way to develop Internet-based, animal care and use oversight training resources for FY01.

III.2.6 Community Visits

Individuals or groups wishing to visit Department facilities need to comply with certain procedural guidelines. All DoD facilities are served by a public affairs office, at either the facility, post, or base. Visits by the public or the press are arranged and coordinated through the appropriate public affairs office. Forty community visits were described in FY00, about the same level of visitation conducted in FY98. The considerably higher visitation rate seen in FY99 (212 visits) was largely due to a change in visitation to a single institution. DoD facilities are visited by various special interest groups including community and civic groups; animal welfare or animal advocates, groups, or individuals; dignitaries, academia, and teachers; local, state, and national politicians; congressional members and staff; and elementary to postdoctoral students. Consequently, a diversified range of individuals is constantly visiting and observing the quality of Department facilities.

III.2.7 Federal Oversight Programs and DoD's Participation

A number of DoD research laboratories participate in the NIH grants process. Institutional compliance with the Public Health Service Policy (PHS Policy) on Humane Care and Use of Laboratory Animals is a prerequisite for granting or continuation of NIH intramural and extramural funding. The formal vehicle for compliance with the PHS Policy is an "Animal Welfare Assurance" negotiated between individual institutions and the Office of Laboratory Animal Welfare (OLAW). The principal references for the negotiation of an OLAW "assurance" are the Health Research Extension Act of 1985 (Public Law 99-158, November 20, 1985, "Animals in Research"), the AWA, and NRC's *Guide for the Care and Use of Laboratory Animals*. Consequently, OLAW provides additional oversight to those laboratories that have negotiated OLAW assurances.

The U.S. Interagency Research Animal Committee (IRAC), established in 1983, serves as a focal point for Federal agencies' discussions of issues involving all animal species needed for biomedical research and testing. The committee's principal concerns are the conservation, use, care, and welfare of research animals. Its responsibilities include information exchange, program coordination, and contributions to policy development. In 1983, the IRAC prepared and promulgated the Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training (U.S. Government Principles).

The DoD provides the DDR&E-designated representative to the IRAC, which is composed of members from all the major government users and regulators of research animals. This participation underscores the DoD's commitment to providing a visible and active presence among other government agencies for the discussion of issues and policies affecting animal research.

The DoD provided an ACLAM board-certified LAM veterinarian to Headquarters, Animal Care, USDA via the U.S. Army Training with Industry Program during FY99-00. This provided an ideal regulatory compliance training opportunity for the officer, as well as for the USDA, which does not have a specialty trained staff veterinarian in LAM. The officer provided input to evolving national level USDA policies and regulations and participated in colloquia on animal use and alternatives use/development for federally mandated animal testing. The officer now fills a regulatory compliance position for the Navy and is the DoD representative to the IRAC.

III.2.8 Additional Oversight

Within the DoD, individuals may raise animal welfare concerns. This may be with the IACUC, facility commanders, the component's IG, or the attending veterinarian. Other means of noncompliance or concern may be voiced through "Waste, Fraud and Abuse Hotlines," or the formal chain of command. Procedures to enhance and facilitate these mechanisms have been implemented in DoD facilities.

The function of the IACUC and the role of an ombudsman are augmented by the component's IG. An ombudsman is defined in Webster's dictionary as "a government official charged with investigating citizens' complaints against the government." The Humane Society of the United States, a witness at the April 7, 1992 hearing on The Use of Animals in Research by the Department of Defense before the House Armed Services Committee, offered the Ombudsman Program at the Massachusetts Institute of Technology as an example of a model program. This program consists of an ombudsman assigned to the university president's office to hear complaints regardless of the nature. These include personnel complaints, sexual harassment, and animal welfare. The DoD assigns this responsibility to its IG and IGs of the military components. In addition, military bases and large organizations on military bases have their own IGs who fulfill this function. Significantly, complaints to an IG can be made anonymously. Also of note is the fact that IG investigations are conducted with complete autonomy and are completely insulated and immune to pressure from the chain of command.

Oversight of extramural (contract) animal-based research is provided for in DoD Directive 3216.1 (Appendix A). As directed by DoD Directive 3216.1, all nonhuman primate protocols receive a headquarters-level administrative review from the appropriate DoD component office. It also states that,

- a. "all extramural research proposals using live animals shall be administratively reviewed by a DoD veterinarian trained or experienced in laboratory animal science and medicine before grant or contract award."
- b. "the most recent [U.S. Department of Agriculture] USDA inspection reports are provided or obtained for the facility under consideration for a research contract or grant using animals, and that during the term of the award, the most recent USDA inspection reports be reviewed on an annual basis."
- c. "a DoD veterinarian trained or experienced in laboratory animal science and medicine shall conduct an initial site visit to evaluate animal care and use programs at contracted facilities conducting DoD-sponsored research using nonhuman primates, marine mammals, dogs, cats, or proposals deemed to warrant review. The initial site visit shall occur within 6 months of when the facility has taken delivery of the animals under DoD contract or grant award. Any facility receiving a DoD-funded grant or contract for animal-based research shall notify the DoD component sponsor and shall have a site inspection within 30 days of notification of loss of AAALAC accreditation for cause, or notification that the facility is under USDA investigation. Site inspections for cause shall evaluate and ensure the adequacy of animal care and use in DoD-sponsored programs, and provide recommendations to the sponsoring DoD component about continued funding support of the research."

III.3 CHAIN OF COMMAND OVER ANIMAL CARE AND USE PROGRAMS

The chain of command is designed to resolve problems at the lowest possible level. It provides control and communication among various components of organizations. Each link in the chain of command is a level of responsibility and authority that extends from the President of the United States, as Commander in Chief, down to the lowest supervisory level. Different levels within the chain have different responsibilities and authority. Each level in the chain is responsible for a lower level and accountable to a higher one. Every individual in the military is part of the chain of command and is accountable to it.

Within the DoD, the chain of command relevant to animal care and use descends from the Secretary of Defense to the Under Secretary of Defense for Acquisition and Technology, to the DDR&E. The DoD Directive 3216.1 designates to the DDR&E all responsibility for animal use oversight. Two advisory bodies are further designated to support the DDR&E in this capacity. The first is the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The second, the Joint Technical Working Group (JTWG) on Animal Use, advises the ASBREM on all animal-related issues. The JTWG membership is principally composed of LAM-certified veterinarians who provide oversight advice on all matters on the care and use of animals for research, education, testing, clinical investigation, or training within the DoD.

All three military departments report to the DDR&E regarding animal use. There are also four DoD Activities that conduct RDT&E or training with animals. The Defense Advanced Projects Research Agency is overseen by the DDR&E (DoD Directive 5134.3). The USUHS is overseen by the Assistant to the Secretary of Defense for Health Affairs (ATSD[HA]) (DoDD 5105.45). The Armed Forces Radiobiology Research Institute is subordinate to USUHS (Program Decision Memorandum, dated September 22, 1992). The DDR&E also oversees these four agencies with respect to their use of animals in RDT&E and training (DoDD 3216.1).

III.4 AVOIDANCE OF UNINTENDED DUPLICATION OF RESEARCH

Both the DoD and Congress have a long history of concern about the potential for unintended duplication of Defense research. Within the past decade, the Department has initiated significant improvements in its mechanisms for coordination, joint planning, and review of its research programs.

In 1981, Congress expressed concerns about the potential for unnecessary duplication of biomedical research among the Military Departments (H.R. 96-1317). This resulted in the DoD proposing the ASBREM Committee coordinate biomedical research planning and the conduct of biomedical research among the Military Departments. Congress fully endorsed and built upon this proposal by establishing DoD Lead Agencies for major elements of the biomedical research programs for which there were either no, or very few, service-unique requirements (H.R. 97-332). For example, the Army was designated the DoD Lead Agency for military infectious disease and combat maxillofacial research while the Navy was designated DoD Lead Agency for preventive and emergency dentistry research. The ASBREM Committee established Joint Technology Coordinating Groups (JTCGs) (Figure III-3), for each major biomedical research program and representatives of biomedical research laboratories, to coordinate all DoD biomedical research planning and execution. The ASBREM Committee process has proven to be highly effective at eliminating unnecessary duplication of biomedical research.

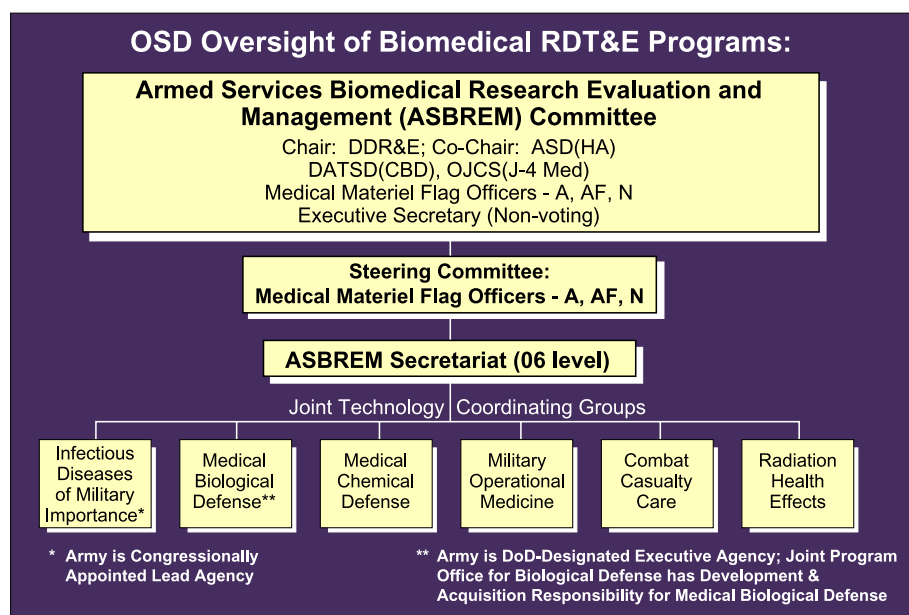


Figure III-3 Structure of ASBREM Committee - Army (A), Air Force (AF), Navy (N)

Because of the wide range of organizations and variations in process between the Military Departments and Defense Components, the DoD uses a variety of mechanisms to coordinate its research and training. The ASBREM Committee process became the model for joint DoD coordination initiatives. Responsibility for joint coordination, planning, execution, and review of the Department's S&T programs was assigned to joint oversight bodies: the Defense Science and Technology Advisory Group (DSTAG), the ASBREM Committee, the Training and Personnel Systems Science and Technology Evaluation and Management (TAPSTEM) Committee, and the Joint Engineers Management Panel. The resulting technology area responsibilities are shown in Figure III-4. The TAPSTEM Committee oversees DoD personnel and training research (Figure III-5) and the Joint Engineers Management Panel oversees environmental quality and civil engineering (Figure III-6). The DSTAG is responsible for general oversight as well as specific joint planning for Combat Materiel (Figure III-7). These oversight bodies are assisted in execution of their responsibilities by subordinate S&T coordinating groups that are focused on coordination of specific technology areas. For example, the ASBREM and TAPSTEM Committees are supported by the JTTCGs, (Figures III-3 and III-5) and Joint Engineers Management Panel, and the DSTAG are supported by separate technology panels (Figures III-6 and III-7). Under this process, researchers and managers from the service laboratories jointly plan, execute, and coordinate their research to minimize redundancy and take advantage of each other's strengths.

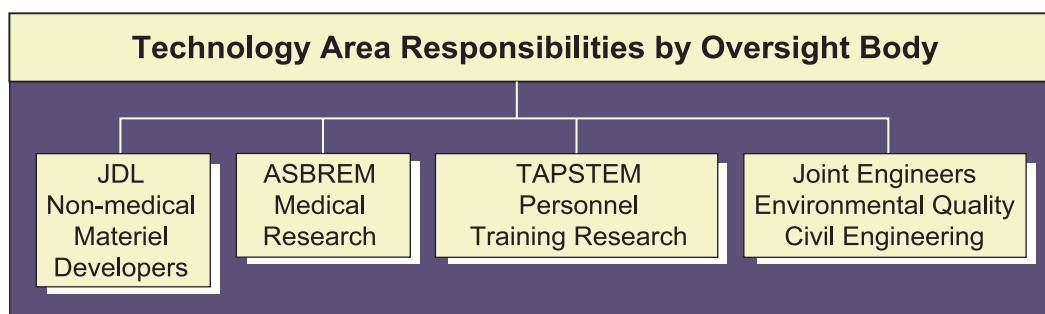


Figure III-4 DoD Technology Area Oversight

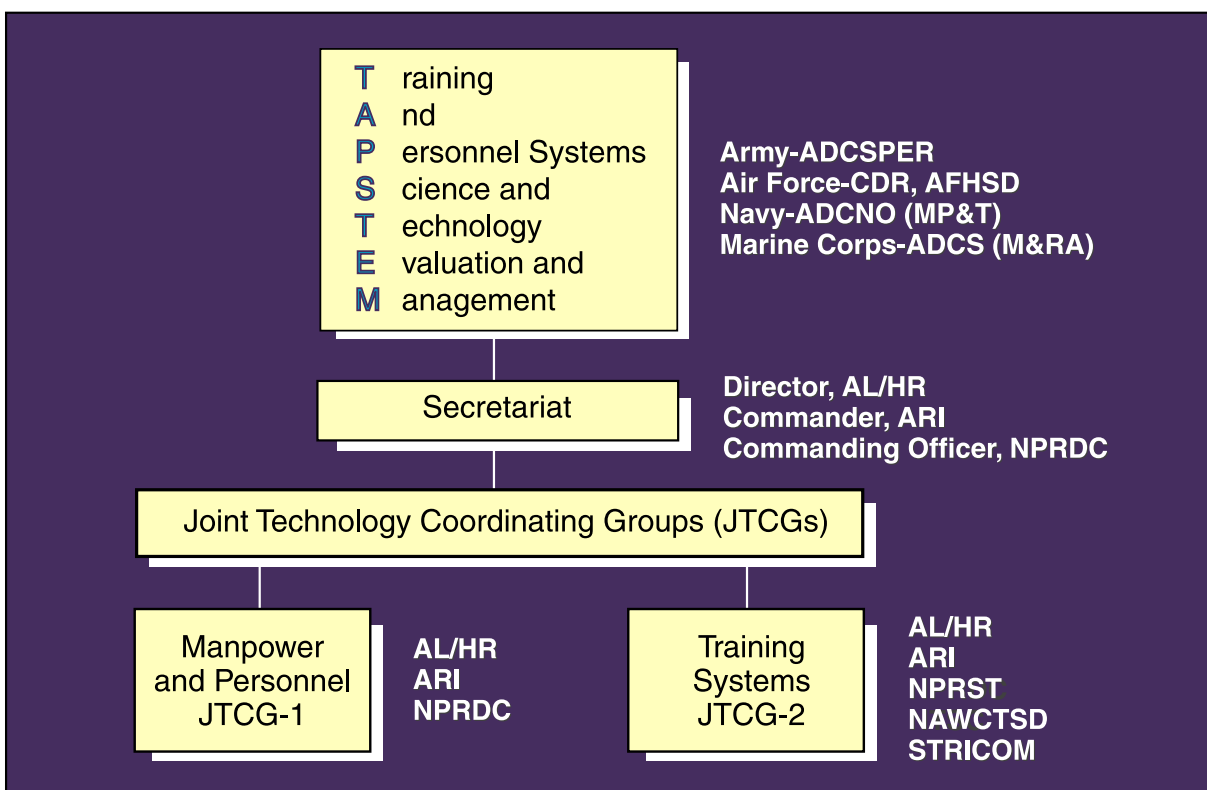


Figure III-5 TAPSTEM Organization

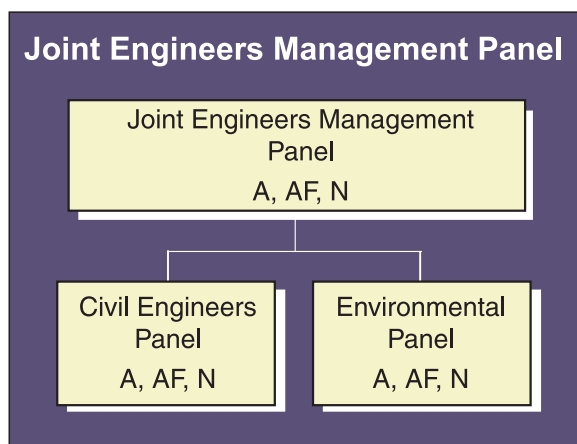


Figure III-6 Joint Engineers Management Panel



Figure III-7 The DSTAG and its Technology Areas

One of the primary ways that the DoD prevents unnecessary duplication is by the use of the DoD SPF (Appendix C). The DoD policy for compliance with Federal regulations and DoD Directive for the care and use of laboratory animals in DoD-sponsored programs (Appendix B) require that all intramural protocols involving animals use the SPF. It also requires that all extramural contractors provide all of the pertinent information contained in the SPF. Until March 2000, the SPF required that the principal investigator perform a literature search of Federal Research in Progress (FedRIP) and Defense Technical Information Center (DTIC) databases or their equivalent to prevent unnecessary duplication of effort. In response to recommendations made by the Government Accounting Office (GAO) in FY00, the SPF requirement was changed to require a search of the BRD and either the FedRIP or the Department of Health and Human Service's CRISP database (Appendix H). An additional search of the scientific literature in databases such as MEDLINE, GRATEFUL MED, MEDLARS, the DTIC database, or the Animal Welfare Information Center is recommended. The principal investigator signs an assurance statement to document that the search was performed.

In addition to these formal coordination and review processes to eliminate research duplication, there are a number of less formal mechanisms that provide significant disincentives for research duplication. Competition, both in-house and extramural, for research support is a prominent feature of S&T; each year large numbers of scientifically meritorious research proposals cannot be funded due to shrinking resources and funding shortages. In most cases, the professional stature of individual scientists or engineers among their peers is measured by their individual and original contributions to the scientific literature. There is little if any reward for unnecessarily duplicating the work of others; such actions often have significant negative impact on how the scientist or engineer is viewed by peers and on the ability to secure research support. Additionally, within the DoD civilian personnel system, scientists' and engineers' pay grades are determined in part by the level of individual scientific and technological contributions. One outcome of research is publication of a manuscript in a professional journal. A sample listing of journals with DoD animal research publications is found in Appendix G. Peer-reviewed journals critique the research during the review process, leading to an overall enhancement of the research process and to validation of both the scientific merit and necessity of the research. These less formal, relatively unquantifiable, disincentives substantially augment and buttress the Department's formal mechanisms for regulating and avoiding unnecessary research duplication within its S&T programs.

III.5 AVOIDANCE OF UNNECESSARY RESEARCH

The same factors that effectively prevent unwarranted duplication of research are applied to prevent unnecessary research. Additionally, through Cooperative Research and Development Agreements, the Department has increased its emphasis on leveraging and exploiting, for Defense needs, S&T investments from other Federal agencies, U.S. industry, academic institutions, and the international scientific community. Past descriptions of Defense S&T "spin-

off” have been supplanted by programs intended to “spin-on” accomplishments by others as well as to optimize the dual-use potential of the Defense S&T investment. The foundation of Defense S&T strategy is the application of S&T accomplishments to sustain Defense technological superiority through efficient and responsive modernization of our warfighting capabilities.

III.6 CONGRESSIONAL OVERSIGHT

In 1999, the GAO completed a programmatic evaluation of the DoD’s FY96 Animal Care and Use Programs (NSIAD/HEHS-99-156 July 8, 1999). The GAO examined animal care and use regulations, policies, procedures, management, and oversight; relevancy of animal-employing research to military objectives; looked for unnecessary duplication of this research; and evaluated the extent of incorporation of alternatives that reduced, replaced, or refined the use of animals. The ultimate outcomes of this evaluation were two modifications to the SPF. First, a change in the literature search requirement was implemented, as noted in section of III.4 of this report. Second, there was a requirement for a listing of all animal use alternatives that were considered. These changes became effective on March 24, 2000 by order of the DDR&E (Appendix H).

III.7 SUMMARY

Research using animals is highly structured and regulated in the United States, being governed by numerous laws, regulations, and policies. These meet and go beyond those established under the AWA (Figure III-8). Consequently, the DoD has a number of stratified formal and informal mechanisms for reviewing, regulating, and executing its animal care and use programs. Research performed by the DoD receives close programmatic, scientific, and regulatory scrutiny, being carefully reviewed by various offices, committees, and program managers before it is funded or implemented. These reviews serve to determine the necessity to the mission, provide oversight of animal care and use, and avoid unnecessary or unintended duplication of research.

Individual IACUCs provide oversight of animal care and use programs and research. They also provide training and information about animal care and use and ensure the humane use of animals in research. Each DoD facility’s IG is also an effective means for investigation of concerns about the necessity of animal use, as well as the ethical treatment and humane care of animals used in DoD research.

DoD policy dictates that all institutions that maintain animal facilities must seek AAALAC accreditation. AAALAC accreditation ensures that DoD laboratories will receive independent evaluation and maintain similar high standards.

Over the past decade, the DoD, in concert with Congress, has streamlined and greatly improved coordination of its S&T activities to avoid unnecessary duplication and provide a focused program of research responsive to the DoD’s unique and wide-ranging needs. When viewed in its totality, the Department’s significant progress and investment in administration, infrastructure, standardization, training, and oversight of animal use are indeed impressive and can serve as useful models for the rest of the animal use research community.

DoD animal use policy is strictly adhered to and exceeds the requirements set forth by the AWA and its implementing regulations.

Notable differences are:

IACUC Composition

- Animal Welfare Regulations require only three members. The DoD requires five.
- The DoD additionally requires one nonscientific member, adding the perspective of a layperson, and ensures that nonaffiliated members are backed up by alternates. Alternate members are also frequently used for other IACUC positions and assume voting responsibilities when regular members are unavailable. Alternate positions are also used to train incoming IACUC members at some institutions.
- The DoD requires AAALAC accreditation for all of its laboratories and facilities that use animals in research or training. Animal Welfare Regulations do not.

Military-Specific Policies

- Policy elements also restrict the use of companion animals and nonhuman primates in DoD research.

Extramural Policies

- All proposals involving animal use by an extramural or a government-contracted institution must be reviewed by a DoD veterinarian.
- Activities in foreign countries are conducted in accordance with both U.S. and host country regulations and, if regulatory differences exist, the more stringent standards are applied.

Animal Species

- The AWA and its implementing regulations do not include birds, or the most commonly used laboratory animals, mice and rats. The DoD uniquely requires full reporting of all mice and rats in terms of numbers and pain category, and requires justification for all animal use that might result in unalleviated pain and distress.
- Special restrictions and oversight requirements also apply to the use of dogs, cats, marine mammals, and nonhuman primates. These animals are limited in terms of the types of research that they can be used with and can require special site visits or approval by special oversight bodies in the case of some nonhuman primates.

Figure III-8 Difference between DoD Animal Use Policies and the Animal Welfare Regulations

SECTION IV

DoD ANIMAL USE PROFILES

The information presented in this section provides profiles on the reported use of animals by component, species, research category, and the U.S. Department of Agriculture (USDA) pain categories of Department of Defense (DoD) animal-based research, testing, and training programs for fiscal year (FY) 2000.

IV.1 METHODS

Information was solicited and received from DoD components and DoD-funded organizations involved in animal care and use programs located both in and out of the United States. These included extramural contractors and grantees that performed animal-based research. For the purpose of this reporting requirement, an intramural program represents research performed at a DoD facility and funded by either DoD or non-DoD funds. An extramural program represents research performed by a contractor or grantee that is funded by the DoD.

IV.1.1 Animal Use Profiles

The animal use profiles prepared for this report are consistent with the reporting information and data provided to the USDA Animal and Plant Health Inspection Service (APHIS) Form 7023. In addition, this report contains comprehensive information on all other animals (e.g., mice, rats, and birds) used that are not required in reports to the USDA.

For the purposes of the FY00 reporting requirement, an animal was defined as any whole nonhuman vertebrate, living or dead, excluding embryos, that was used for research, development, test, and evaluation (RDT&E) and training. Only live animals or whole dead animals, as defined, that were either on hand in the facility or acquired and used during FY00 are included. Animal organs, tissues, cells, blood, fluid components, and/or by-products purchased or acquired as such animal/biological components are not reported. This definition does not include animals used or intended for use as food for consumption by humans or animals, animals used for ceremonial purposes, or military working animals and their training programs.

A single animal was counted only once in determining the number of animals used during the fiscal year for a particular work unit or protocol. This does not refer to the number of times an individual animal was injected, manipulated, handled, or administered medication and/or experimental compounds within a given work unit, protocol, or program. Animals on hand during FY00 but not actually used during the fiscal year are not included in this number.

IV.1.2 Animal Use Categories

All DoD components and extramural organizations involved in the performance and/or funding of animal care and use programs reported animal work by the category that best describes the general research purpose of the animal use. The 8 general categories and 23 specific subcategories are listed in Table IV-1. If the research categories provided did not adequately describe the animal use within each particular work effort, the animal was placed in the Other category. In-depth information on specific activities performed within a subcategory is presented in Appendix N. The medical research categories correspond to the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee's Joint Technology Coordinating Group Medical Research Areas. Nonmedical categories consist of RDT&E programs performed outside the ASBREM Committee medical oversight. Clinical Investigations studies were performed under the auspices of the Assistant Secretary of Defense for Health Affairs and the military services medical departments through Major Force Program 8 funding. These studies were usually in support of graduate medical education training programs located at the major military medical centers.

Table IV-1 Animal Use Categories

<p>MEDICAL (M)</p> <p>M1: Military Dentistry M2: Infectious Diseases M3: Medical Chemical Defense</p> <p>M4: Medical Biological Defense M5: Human Systems Technology M6: Combat Casualty Care M7: Ionizing Radiation M8: Other Medical RDT&E</p> <p>NONMEDICAL (N)</p> <p>N1: Physical Protection N2: Physical Detection N3: Offensive Weapons Testing N4: Other Nonmedical RDT&E</p> <p>CLINICAL INVESTIGATIONS (C)</p> <p>C1: Clinical Medicine C2: Clinical Surgery C3: Other Clinical Investigations</p>	<p>TRAINING/INSTRUCTIONAL (T)</p> <p>T1: Training, Education, and/or Instruction of Personnel T2: Other Training/Instruction</p> <p>ADJUNCTS/ALTERNATIVES TO ANIMAL STUDIES (A)</p> <p>A1: Adjuncts to Animal Use Research A2: Alternatives to Animal Investigation A3: Other Alternatives/Adjuncts</p> <p>CLASSIFIED SECRET OR ABOVE STUDIES (S)</p> <p>Classified secret or above studies on animals</p> <p>ANIMAL BREEDING STOCK (B)</p> <p>Animals maintained for breeding</p> <p>OTHER ANIMAL USE CATEGORIES (O)</p> <p>Other animal use purposes</p>
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IV.1.3 USDA Pain Categories

The USDA requires that all institutions using any regulated animal for research, testing, training, or experimentation register with the USDA as a research facility and submit an annual report. This annual report presents with other animal use information the number of animals used by species and the USDA pain category, if any, to which the animals were exposed. The report includes all animals used by the DoD, including animal species that are not regulated by the AWA and its implementing regulations.

The USDA has developed three pain/distress categories for its reporting requirement (Table IV-2). All animals herein reported are assigned to one of the three USDA pain categories; this includes animals that are not regulated by the USDA. The USDA requires that any reporting program that uses procedures producing unalleviated pain or distress file an explanation of the procedures and the reasons that the pain/distress was not relieved in the annual USDA APHIS report.

Table IV-2 USDA Pain Categories
(USDA APHIS Form 7023)

<p>USDA COLUMN C</p> <p>Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.</p> <p>USDA COLUMN D</p> <p>Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.</p> <p>USDA COLUMN E</p> <p>Number of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests.</p>

The animals reported in Column C of the USDA report are those used in a procedure that would reasonably be expected to cause not more than slight or momentary pain and/or distress in a human being to which that procedure was applied. Procedures performed on these animals are those that are usually conducted on humans without anesthesia or analgesia. Examples include most blood-sampling techniques (excluding intracardiac blood sampling), injections, and tattooing.

The animals reported in Column D of the USDA report are those in which pain is alleviated by appropriate anesthetic, analgesic, or tranquilizing drugs. Examples include anesthesia for surgical procedures or catheter placement, and analgesia during recovery from surgery.

The animals reported in Column E of the USDA report are those that would experience more than slight or momentary pain or distress that cannot be alleviated by drugs. Examples of procedures where drugs were not used because they would have adversely affected the procedures, results, or interpretation of the research, or tests include some infectious disease studies and some toxicology studies.

All procedures that involve animals in USDA Pain Category Columns D or E are extensively reviewed during the protocol approval process. Prior to formal protocol review, a veterinarian with experience and/or training in laboratory animal medicine must review all procedures. In addition, the primary investigator must write a justification for all procedures for animals in Column E. The DoD standard protocol states, "Procedures causing more than transient or slight pain that are unalleviated must be justified on a scientific basis in writing by the primary investigator. The pain must continue for only the necessary period of time dictated by the experiment, and then be alleviated, or the animal humanely euthanized." Moreover, the primary investigator must sign an assurance statement that alternative procedures are not available, and the Institutional Animal Care and Use Committee must review and approve all procedures before the study begins.

IV.2 RESULTS/DISCUSSION

IV.2.1 General Results

There was a total of 365,803 animals reported used in FY00, which is a 12% increase from FY99 and a 34% (187,897) decrease from FY93 (Figure IV-1). In accordance with the AWA and its implementing regulations, animals are defined as "any live or dead dog, cat, monkey (nonhuman primate (NHP) mammal), guinea pig, hamster, rabbit, or such other warm-blooded animal, as the Secretary may determine." Therefore, only 7% (26,041) of the animals reported used by the DoD in FY00 are considered USDA reportable species.

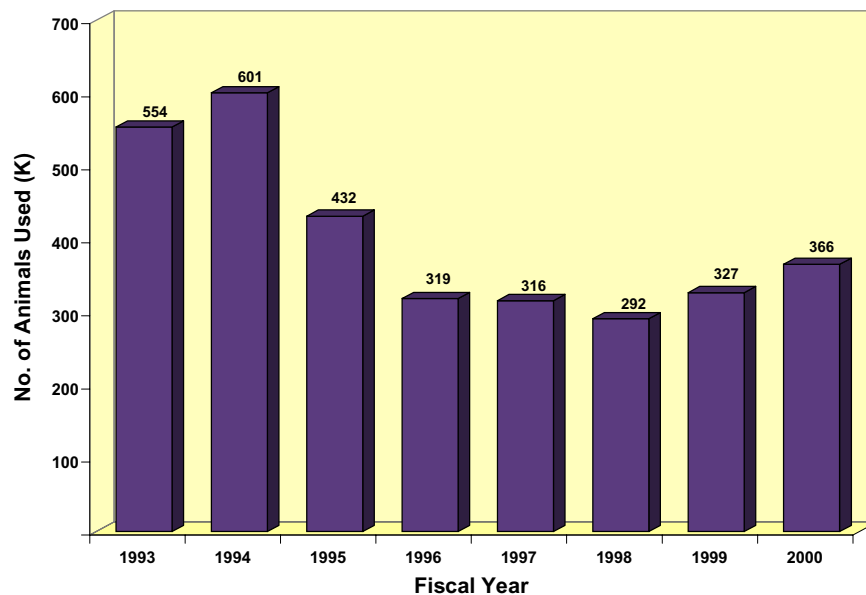


Figure IV-1 DoD Animal Use by Year

In FY00, 187,234 animals were reported used in intramural research programs and 178,569 were used in extramural grants or contracts (Figure IV-2). Reported intramural animal use decreased by less than 1% (23) in FY00 compared with FY99 use and decreased by 30% (80,857) compared with FY94 use.

The number of animals reported used in extramural research was 28% (38,729) higher in FY00 than the number in FY99 and 46% (154,023) less than the number used in FY94. Extramural programs fluctuate in the number of animals used from year to year due to changes in the number of contracts and grants awarded.

Fluctuations in extramural animal use may result from several factors. First, many extramural research projects only use animals during a portion of the proposed project (e.g., third year of project) and still others use animals throughout the entire project. In addition, the level of funding for extramural programs varies from year to year, thereby changing the total number of extramural projects. Some extramural research programs are congressionally mandated such as Breast Cancer, Gulf War Illnesses, Neurofibromatosis, and Osteoporosis Research Programs; their funding is dependent on yearly congressional appropriations.

IV.2.2 Animal Use by Component

Information concerning total reported DoD use of animals by each component is presented in Figure IV-3. Figures IV-4 and IV-5 show the intramural and extramural animal use by component, respectively.

In FY00, the Army used 68% of the total number of animals reported used by the DoD, 55% of the total intramural animals, and 81% of the total extramural animals. Overall the Army's animal use increased by 21% between FY99 and FY00. The majority of this increase (78%) was in the extramural programs where there was a 30% increase (33,891) in the Army's reported extramural animal use. There was also a 10% (9,628) increase in the Army's intramural animal use since FY99.

The extramural increase primarily came from the Breast Cancer Research Program (9,657), Prostate Cancer Research Program (9,796), Neurotoxin Research Program (7,365), and Bone Health/Osteoporosis Research Program (7,003). Table IV-3 shows the congressionally directed research programs that the Army manages. These programs used the majority (81% or 117,953) of the Army's extramural research animals and 32% of the total DoD animal use in FY00. The Breast Cancer Research Program alone accounts for 17% (61,164) of all of the animals used by the DoD in FY00. The U.S. Army is also the congressionally mandated Lead Agency for infectious disease and military dentistry research and the DoD Executive Agency for medical chemical and biological defense and nutrition studies. The number of animals the

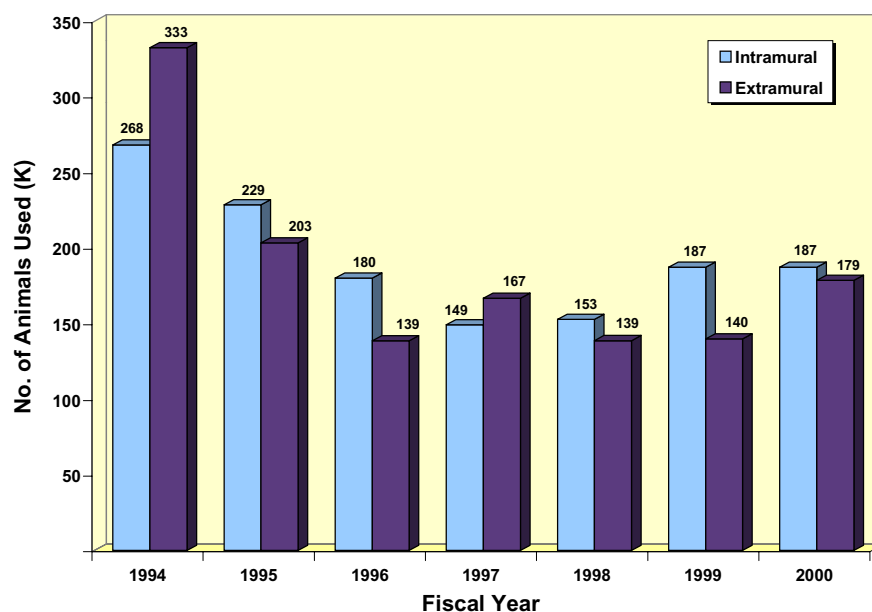


Figure IV-2 Intramural/Extramural Animal Use by Year

Table IV-3 Army's Congressionally Directed Research Programs

Army's Congressionally Directed Research Programs
Bone Health Research
Breast Cancer Research
Defense Women's Health Research
Disaster Relief and Emergency Medical Services
Free Electron Laser
Gulf War Illnesses
Laser Research
Neurofibromatosis Research
Neurotoxin Research
Ovarian Cancer Research
Prostate Cancer Research
Defense Health Research Program

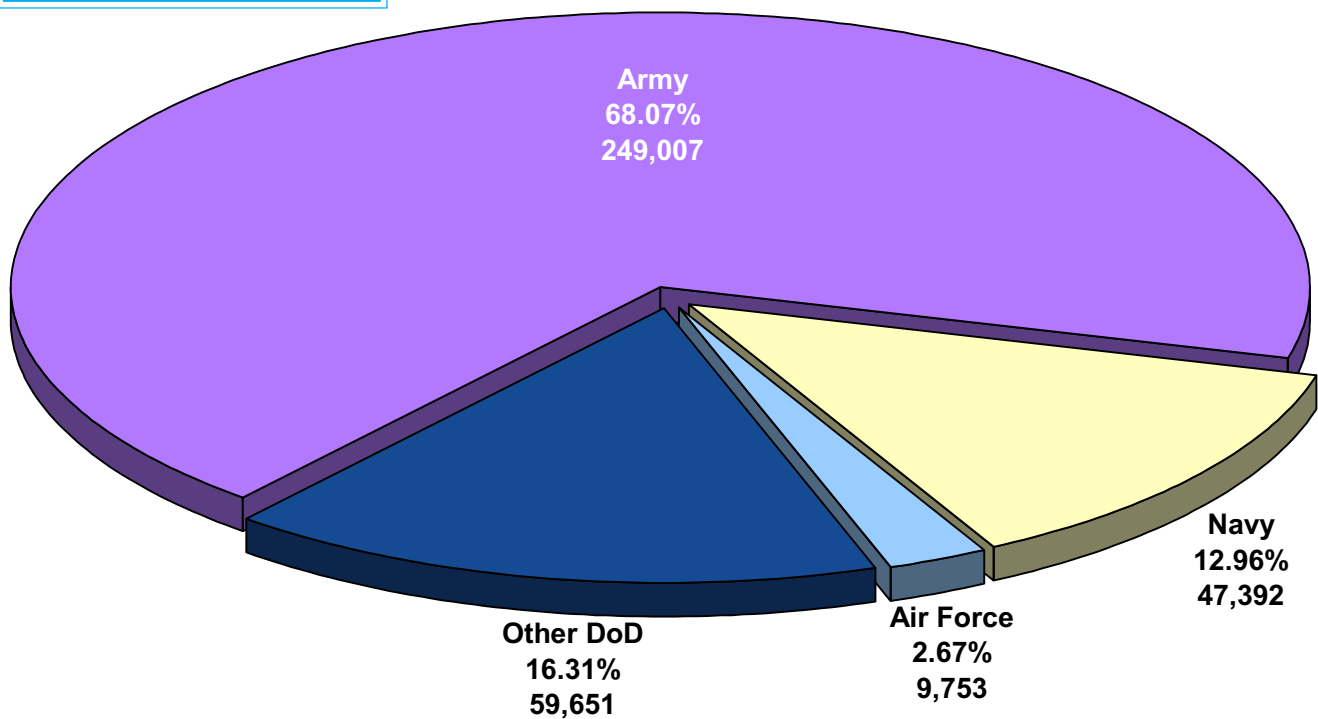
TOTAL = 365,803

Figure IV-3 DoD Intramural and Extramural Animal Use by Service for FY00

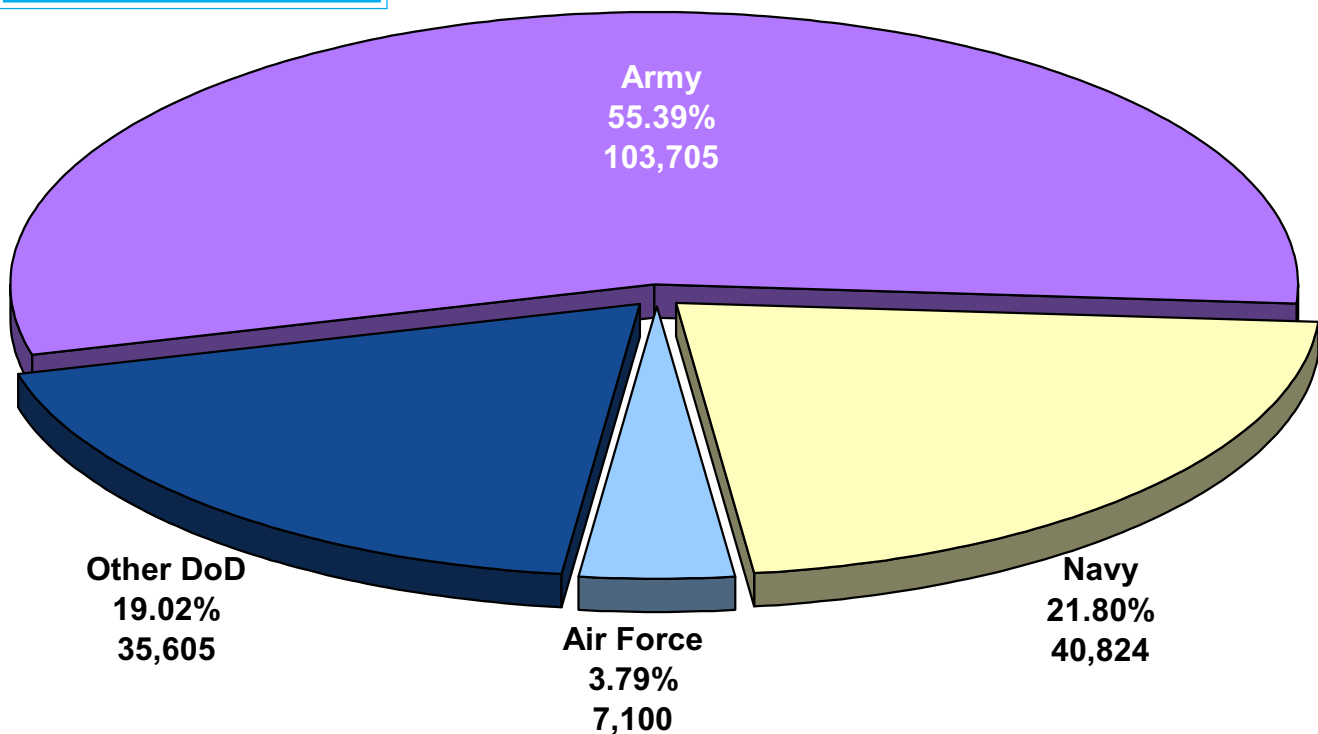
TOTAL = 187,234

Figure IV-4 DoD Intramural Animal Use by Service for FY00

Percentages may not add up to 100% due to rounding of calculations

TOTAL = 178,569

Percentages may not add up to 100% due to rounding of calculations

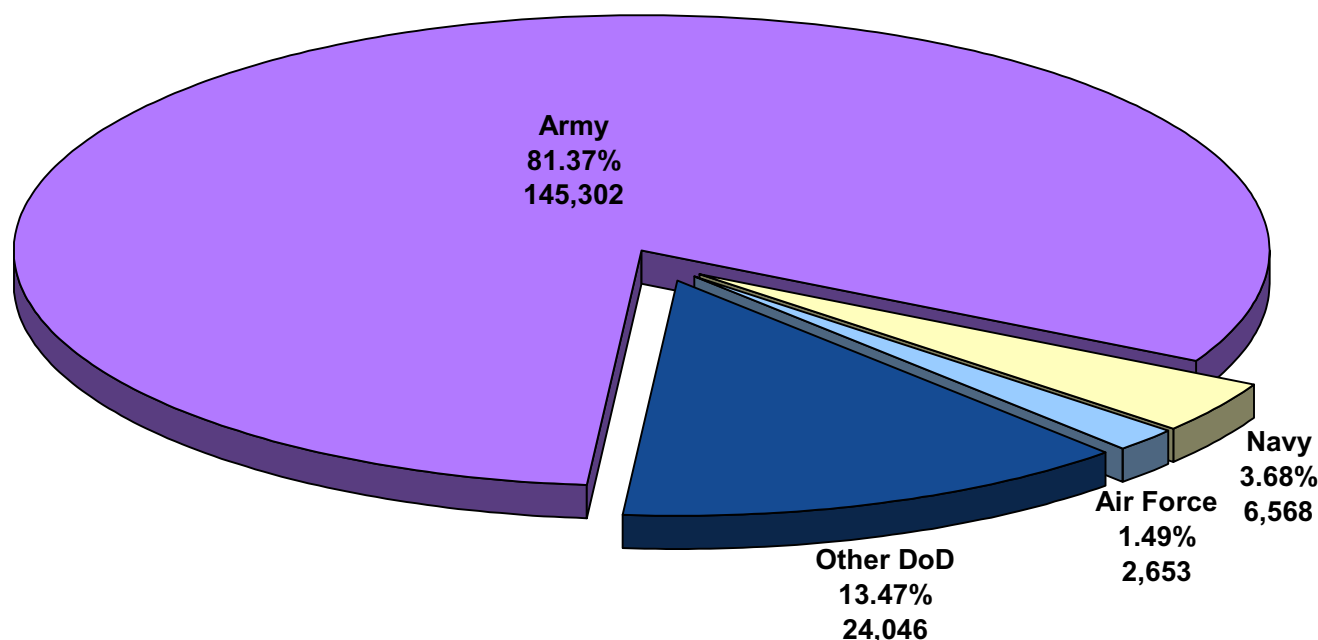


Figure IV-5 DoD Extramural Animal Use by Service for FY00

Army used in research on infectious diseases and chemical and biological defense were 27,606 and 65,794, respectively. Since FY94, the Army has decreased its intramural use of animals by 38% (62,955). At the same time there has been an increase in extramural programs by 50% (146,961). Overall the Army has decreased its use of animals in research by 46% since FY94.

The Navy used 13% of the total number of animals reported used by the DoD, 22% of the intramural animals, and 4% of extramural animals. Comparing reported animal use in FY00 with use in FY99, there was a 33% decrease in the total number of animals used by the Navy. This decrease is attributable to fewer animals used in many intramural research projects (a 38% decrease, numbering 25,332 animals), specifically by infectious disease research which accounts for 21,763 fewer animals used. In FY99, the Navy experienced dramatic change in the use of animals due to the implementation of the Global Emerging Infectious Systems (GEIS) program. The GEIS program was the result of a Presidential Decision Directive NSTC-7 in June 1996 that formally directed all Federal agencies to cooperate in surveillance and research on new infectious disease problems. Because of its wide-ranging assets for disease control, the mission of the DoD, specifically the Navy, was expanded to support global surveillance, training, research, and response to emerging infectious diseases. This decrease in the use of animals in FY00 within the Navy's infectious disease research may be the result of the completion of protocols supporting the GEIS program. Meanwhile the Navy's extramural projects increased animal use by 2,339. The majority of animals (90%) used by the Navy in FY00 were in medical research. Infectious disease and combat casualty care research accounted for 80% and 10% of the Navy's animal use, respectively. Since FY94, the Navy has increased its animal use over the long term by 6% (2,591) primarily in the area of infectious disease research.

The Air Force used 3% of the total number of animals reported used by the DoD, 4% of the intramural animals, and 2% of the extramural animals. The Air Force intramural animal use increased by 1,368, and the extramural animal use decreased by 8,533 resulting in a 7,165 overall decrease in the number of animals used in research in FY00 compared with FY99. The Air Force used 69% and 11% of its animals in nonmedical research and clinical investigation projects, respectively. The majority of animals used in nonmedical research were in physical protections (2,211) and toxicology (2,644). Overall since FY94, the Air Force has demonstrated a 74% decrease (28,225) in the use of animals in research.

The Office of the Secretary of Defense (OSD) components are the Uniformed Services University of the Health Sciences, Defense Advanced Research Projects Agency, Armed Forces Radiobiology Research Institute, and Armed Forces Institute of Pathology. OSD components used 16% of the DoD total animals, 19% of the total intramural animals, and 14% of total extramural animals. There was a 74% (25,345) increase in the use of animals for the OSD components in FY00 compared with FY99. This increase was seen in both the intramural (14,313) and extramural (11,032) programs. The intramural increase occurred in biological defense and ionizing radiation research. Overall the OSD components used the majority (92%) of their animals in clinical investigations (10,714) and medical research (47,065). The majority of clinical research animal use was in clinical medicine projects (7,104). The biological defense (26,165) and ionizing radiation research programs (14,135) accounted for the majority of the OSD components animal use in medical research. Since FY94 there has only been a 1% (670) increase in the OSD components animal use.

IV.2.3 Animal Use by Species

The DoD has developed three major classifications for reporting animal use: non-mammals, rodents, and other mammals. Rodents are the primary type of animals used for each research category and accounted for 91% of the DoD's animal use in FY00. This year the use of rodents increased by 47,942 (Figure IV-6) which was a 15% (35,755) increase in the use of mice and a 37% (11,415) increase in rats. At the same time, there was a decrease in the use of gerbils (48), shrews (69), and squirrels (30). Compared with FY99, in FY00 there was a 30% (9,072) decrease in the reported use of non-mammals and a 1% (164) decrease in the number of other mammals used. The vast majority (96%) (350,970) of animals used by the DoD in FY00 were rodents, birds, amphibians, reptiles, and fish.

Since FY94, there have been significant decreases in the reported use of many species of animals by the DoD. There has been an 85% (118,084) decrease in non-mammals, a 26% (115,023) decrease in rodents, and a 13% (1,773) decrease in other mammals. Several animals used in FY94 were not used at all in FY00 and are shown in

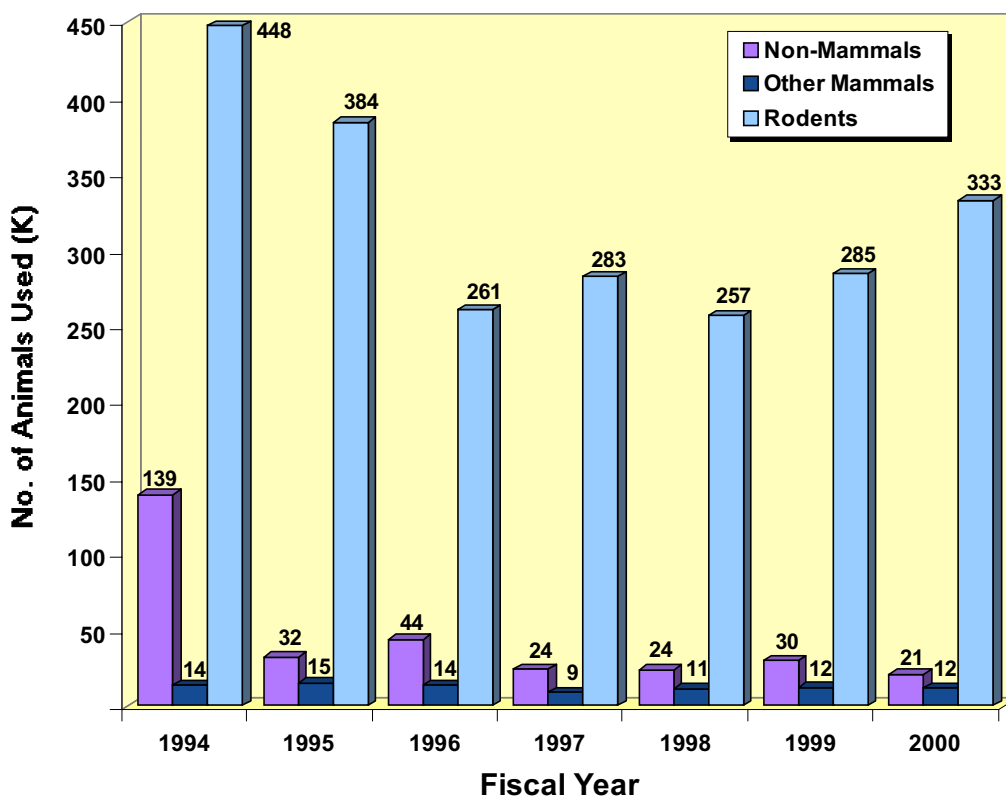


Figure IV-6 Animal Use

Table IV-4. There have been significant decreases in the use of large animals such as marine mammals, horses, sheep, and goats. For example, between FY94 and FY00, there was a 59% (65) decrease in marine mammals and many species were not used in FY00 (Table IV-4). There was also a decrease in the use of horses (103), goats (1,547), and sheep (154). At the same time, there were increases in the use of swine (824), chinchillas (201), bats (348), degu (12), guinea pigs (74), ferrets (15), and reptiles (49). Overall, there has been a shift from the use of large animals to smaller animals and a shift to those that are lower on the phylogenetic scale.

In FY00, there was an increase in the combined use of NHP, dogs, and cats. When comparing FY99 to FY00, there was an increase in the use of NHP (12), dogs (171), and cats (89) (Figure IV-7). Nonhuman primates were primarily used in medical research (81%), and within medical research, they were used in infectious diseases (28%), biological/chemical defense (26%), and human systems technology (13%). The majority of dogs (59%) and cats (85%) were used in medical research. Dogs were specifically used in combat casualty care (18%) and zoonosis (23%). Cats were used in zoonosis (85%).

Table IV-4 Animals Used by the DoD in FY94 and not in FY00

Non-Mammals	Other Mammals
Amphibian	Armadillo
African Toad	Burro
Salamander	Civet
	Fox
	Opossum
Avian	
Duck	Marine Mammal
Falcon	Beluga Whale
Pigeon	Bottlenose Dolphin
Robin	Commersons Dolphin
Sparrow	Common Dolphin
Starling	Elephant Seal
	False Killer Whale
Other Non-Mammal	Fin Whale
Lobster	Gray Whale
Chameleon	Harbor Seal
	Pilot Whale
Reptile	Risso's Whale
Lizard	White-Sided Dolphin
Rodents	
Prairie Dog	

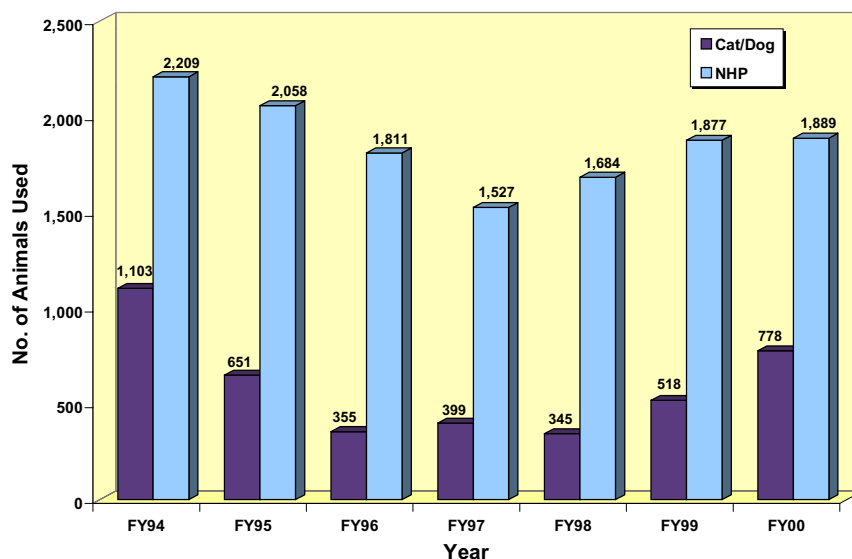


Figure IV-7 Use of Nonhuman Primates and Dogs and Cats by Year

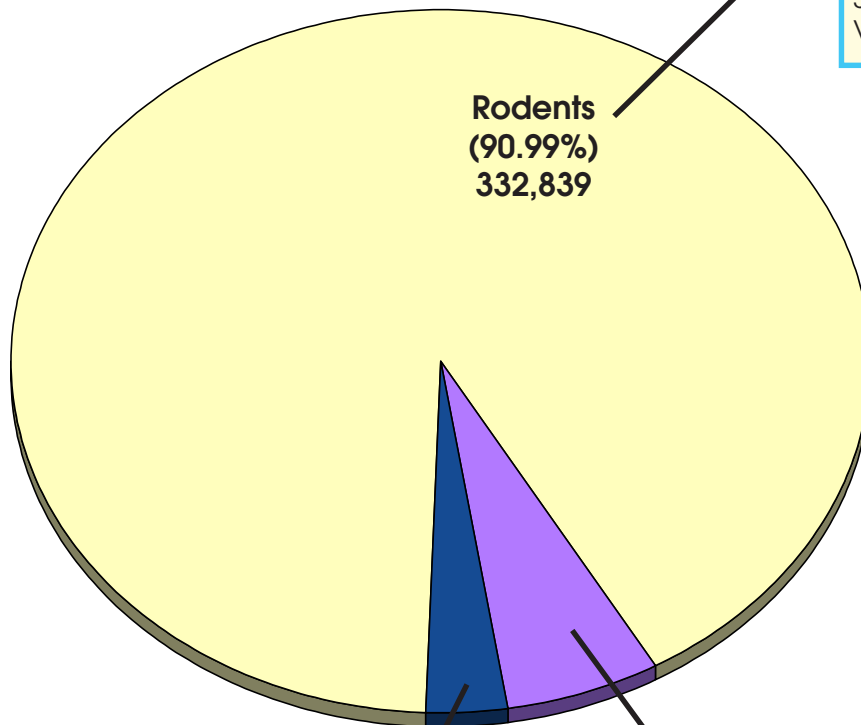
Even with the small increase in the use of NHP this year, there has been a 15% (320) decrease in their use since FY94. During the same time, the use of dogs has decreased 29% (267) and the use of cats decreased 33% (58). This illustrates the Department's continuing commitment to reducing the use of specific species in research.

DoD animal use by species is presented in Figure IV-8. Figures IV-9 and IV-10 represent the intramural and extramural animal use by species for FY00.

TOTAL = 365,803

Percentages may not add up to 100% due to rounding of calculations

Chinchilla	265	(0.07%)
Chipmunk	14	(0.00%)
Degu	12	(0.00%)
Gerbil	9	(0.00%)
Guinea Pig	7,533	(2.06%)
Hamster	3,284	(0.90%)
Mouse	279,019	(76.28%)
Rat	42,577	(11.64%)
Shrew	19	(0.01%)
Squirrel	2	(0.00%)
Vole	105	(0.03%)



**Other Mammals
(3.29%)
12,408**

Bat	348	(0.10%)
Cat	117	(0.03%)
Cow/Bull	155	(0.04%)
Deer	12	(0.00%)
Dog	661	(0.18%)
Ferret	248	(0.07%)
Goat	2,169	(0.59%)
Horse	2	(0.00%)
Marine Mammal	46	(0.01%)
Nonhuman Primate	1,889	(0.52%)
Pig/Swine	2,828	(0.77%)
Rabbit	3,318	(0.91%)
Sheep	255	(0.07%)

**Non-Mammals
(5.72%)
20,916**

Amphibian	537	(0.15%)
Avian	3,703	(1.01%)
Fish	16,619	(4.54%)
Reptile	57	(0.02%)

Avian include: Bird (918), Chicken (2,750), Goose (35)

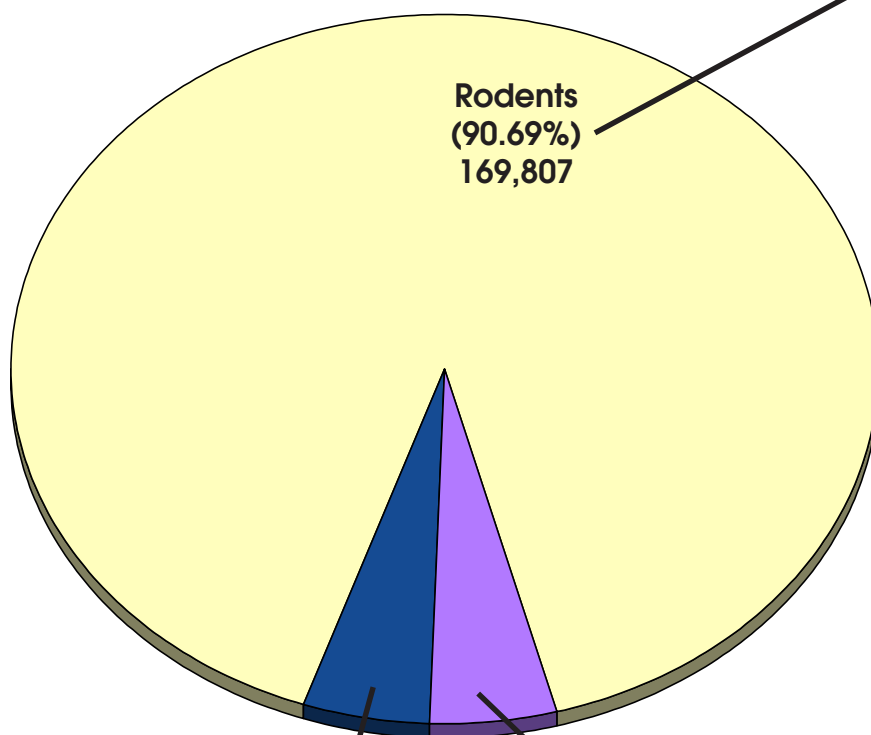
Marine Mammals include: Dolphin (33), Sea Lion (10), Seal (2), Whale (1)

Figure IV-8 DoD Intramural and Extramural Animal Use by Species for FY00

TOTAL = 187,234

Percentages may not add up to 100% due to rounding of calculations

Chinchilla	255	(0.14%)
Gerbil	9	(0.00%)
Guinea Pig	5,664	(3.03%)
Hamster	2,096	(1.12%)
Mouse	141,650	(75.65%)
Rat	20,083	(10.73%)
Vole	50	(0.03%)



Cat	117	(0.06%)
Cow/Bull	129	(0.07%)
Deer	12	(0.01%)
Dog	364	(0.19%)
Ferret	248	(0.13%)
Goat	2,140	(1.14%)
Horse	2	(0.00%)
Marine Mammal	37	(0.02%)
Nonhuman Primate	1,452	(0.78%)
Pig/Swine	1,985	(1.06%)
Rabbit	2,151	(1.15%)
Sheep	132	(0.07%)

Marine Mammals include: Dolphin (33), Sea Lion (3), Whale (1)

Amphibian	205	(0.11%)
Avian	591	(0.32%)
Fish	7,860	(4.20%)
Reptile	2	(0.00%)

Avian include: Bird (484), Chicken (72), Goose (35)

Figure IV-9 DoD Intramural Animal Use by Species for FY00

TOTAL = 178,569

Percentages may not add up to 100% due to rounding of calculations

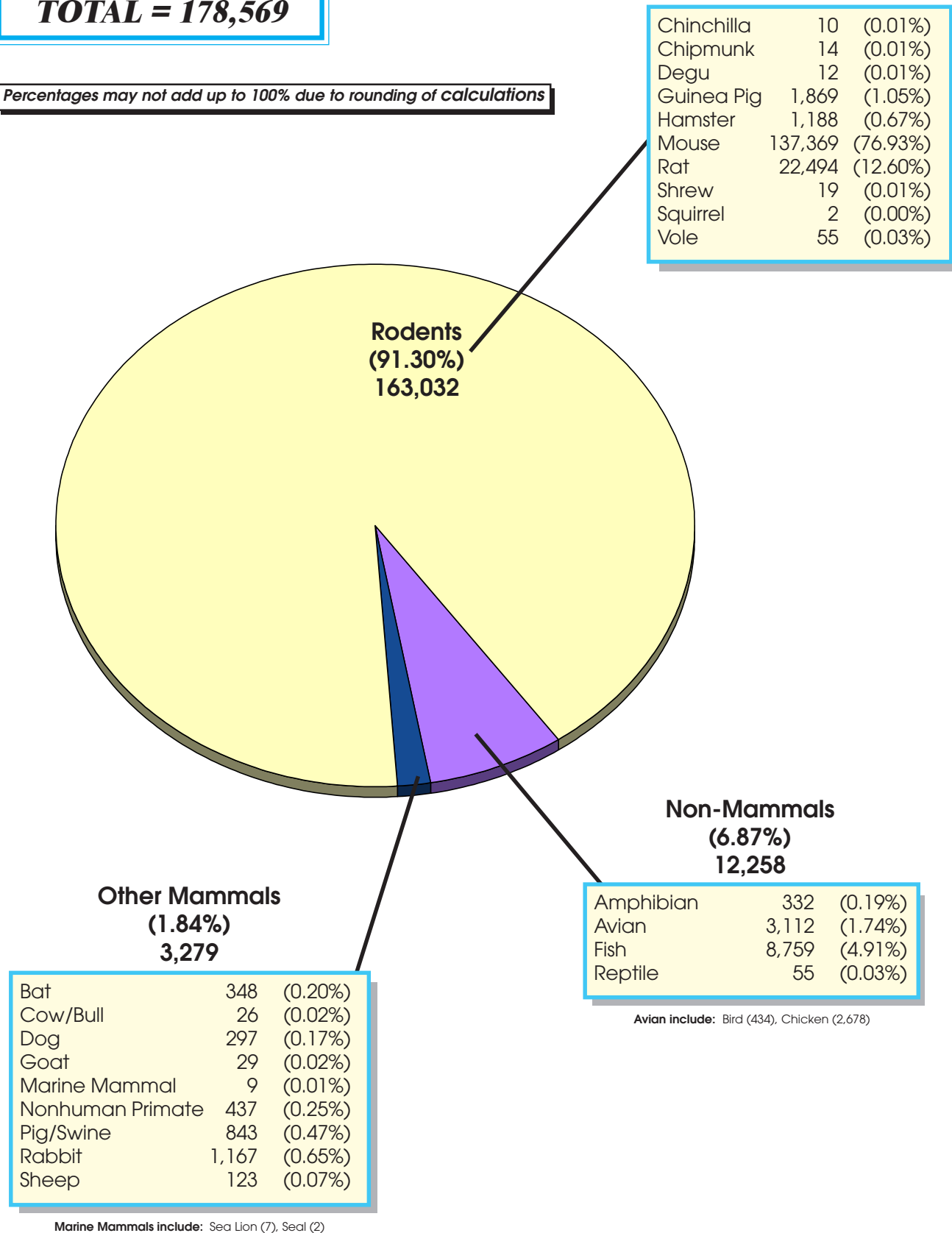


Figure IV-10 DoD Extramural Animal Use by Species for FY00

IV.2.4 Animal Use by Research Category

Total reported animal use in the DoD by research category is presented in Figure IV-11, with the intramural and extramural breakouts in Figures IV-12 and IV-13, respectively (see Appendix N for research category definitions).

The DoD has a critical and challenging mission: to discover, design, and develop military countermeasures against threats to the health and survivability of military personnel. In order to meet this mission, 85% of the animals used by the DoD in FY00 were in medical research. Twenty-three percent (71,933) of the animals used in medical research were in the area of infectious diseases (M2) and of those, 98% (70,398) were rodents (Appendix O). The primary thrust of this research is the development of preventive measures against infectious disease through discovery, design, and development of prophylactic, therapeutic, and treatment drugs for relevant diseases. The chemical defense research program (M3) used 4% (12,971), and the biological defense research program (M4) used 23% (71,933) of the medical research animals. Medical/chemical defense develops improved pretreatments, therapeutics and diagnostics to protect the warfighter from exposure to chemical warfare agents. Medical biological defense develops, demonstrates, and fields new vaccines, drugs, and diagnostic kits for the prevention, treatment, and diagnosis of biological warfare agents. This research program protects the armed forces from the consequences of exposure to biological warfare agents and enhances their survivability.

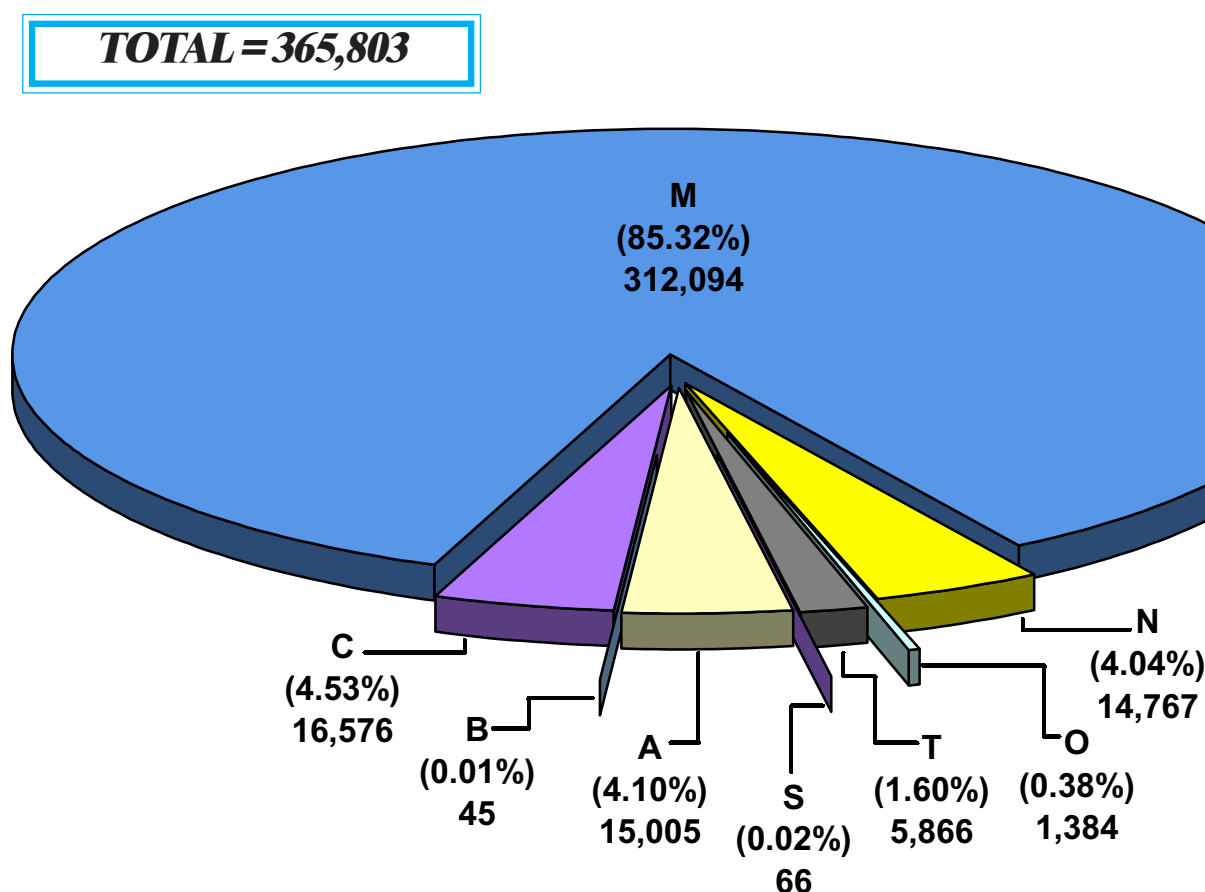


Figure IV-11 DoD Intramural and Extramural Animal Use by Research Category for FY00

A: Adjuncts/Alternatives to Animal Studies, B: Animal Breeding Stock, C: Clinical Investigations, M: Medical RDT&E, N: Nonmedical RDT&E, O: Other Animal Use, S: Classified Secret or above, T: Training & Instructional.

Percentages may not add up to 100% due to rounding of calculations.

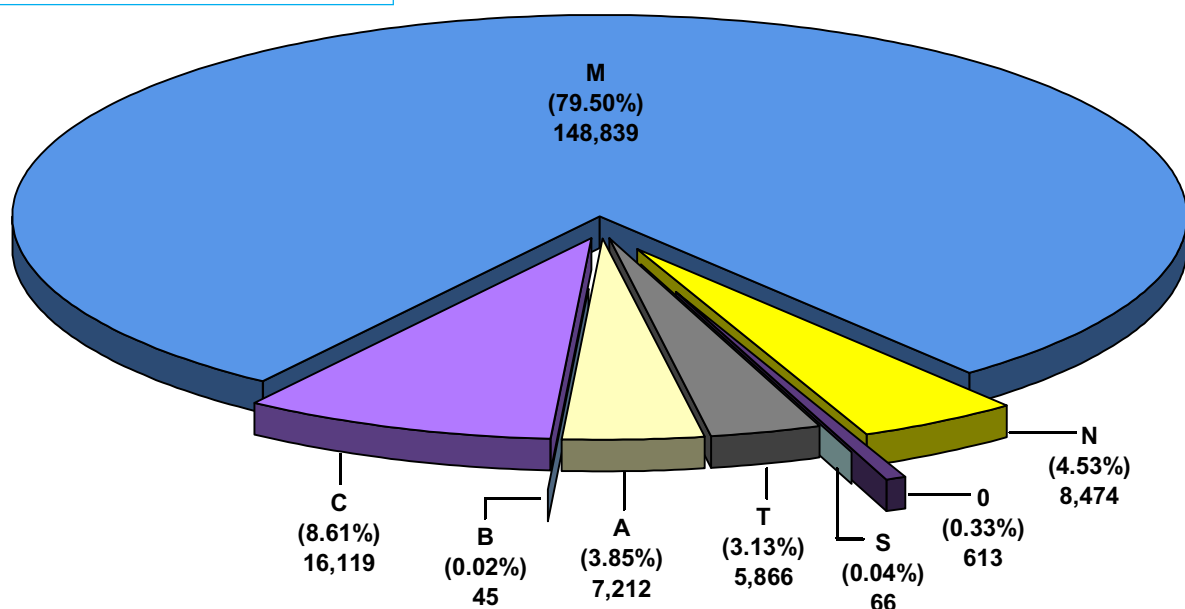
TOTAL =187,234


Figure IV-12 DoD Intramural Animal Use by Research Category for FY00

A: Adjuncts/Alternatives to Animal Studies, B: Animal Breeding Stock, C: Clinical Investigations, M: Medical RDT&E, N: Nonmedical RDT&E, O: Other Animal Use, S: Classified Secret or above, T: Training & Instructional.

Percentages may not add up to 100% due to rounding of calculations.

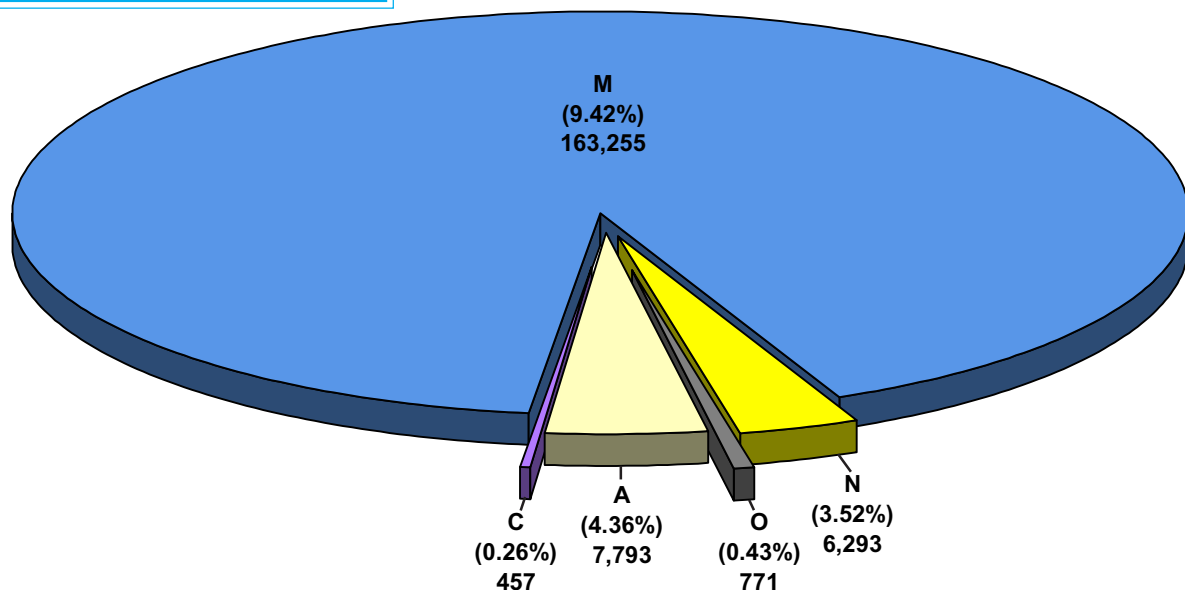
TOTAL =178,569


Figure IV-13 DoD Extramural Animal Use by Research Category for FY00

A: Adjuncts/Alternatives to Animal Studies, B: Animal Breeding Stock, C: Clinical Investigations, M: Medical RDT&E, N: Nonmedical RDT&E, O: Other Animal Use, S: Classified Secret or above, T: Training & Instructional.

Percentages may not add up to 100% due to rounding of calculations.

M8 (Other Medical Research) accounted for 39% of the total medical research category (Figure IV-14). The Congressionally Directed Medical Research Programs shown in Table IV-3 used 119,223 animals in FY00. These programs accounted for 98% of M8 animals (Table IV-5), 38% of the animals used in medical research, and 33% of the total DoD animals used which is a 9% increase from FY99. These types of research programs can cause fluctuations in the total number of animals used from year to year depending on congressional funding levels and direction. Other areas of research within M8 are shown in Table IV-5.

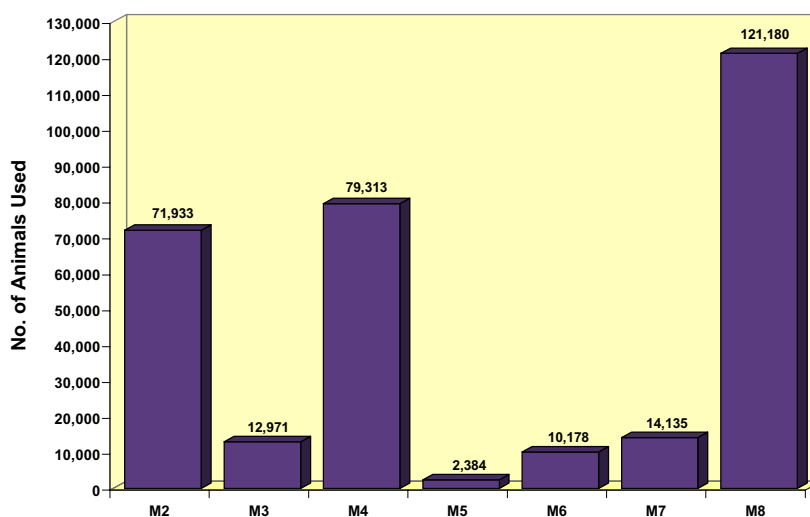


Figure IV-14 Animal Use by Medical Research Category

Clinical research accounted for 5% (16,576) of the animals used by the DoD in FY00. Studies in this category address clinical medicine and surgical problems for the treatment of both diseases and combat casualties. Sixty-seven percent of the animals used in clinical research were used in clinical medicine studies. While many of these conditions are unique to the military, several are not. Specific types of clinical studies are listed in Appendix N.

Nonmedical RDT&E animal use decreased by 24% (4,755) in FY00 and accounted for 4% of the total animal use. Research in the area of alternatives to the use of animals accounted for 4% of the total animal use for FY00 and illustrates the Department's continuing initiatives to promote research to develop alternatives to reduce, replace, and refine the use of animals in DoD research. No animals were reported as used for offensive weapons testing during FY00.

Table IV-5 Breakout of Animals Used in the Research Category M8

Results		
Research Category(M8)	Animals Used	% of M8
Other Medical RDT&E	336	0.28%
Bone Health Research	151	0.13%
Breast Cancer Research	61,164	50.80%
Defense Women's Health Research	47	0.04%
Disaster Relief And Emergency Medical Services	754	0.63%
Environmental Safety	489	0.41%
Free Electron Laser	474	0.39%
Gulf War Illnesses	3,256	2.70%
Neurofibromatosis Research	6,334	5.26%
Neurotoxin Research	10,656	8.85%
Occupational Medicine	6	0.01%
Osteoporosis	9,755	8.10%
Ovarian Cancer Research	1,860	1.55%
Prostate Cancer Research	23,947	19.89%
Toxicology	930	0.77%
Zoonosis	1,021	0.85%
TOTAL	121,180	

Percentages may not add up to 100% due to rounding of calculations

Two percent of the animals used by the DoD in FY00 were in the training, education, and instruction of personnel. Training and instruction are basically for animal technicians and medical personnel (Appendix N). Breeding stock, classified studies, and other studies each accounted for less than 1% of the DoD's total animal use in FY00.

IV.2.5 Animal Use by USDA Pain Category

Total reported animal use in the DoD by USDA pain category is presented in Figure IV-15, with the intramural and extramural breakouts in Figures IV-16 and IV-17, respectively.

The majority (86%) of research employing animals in the DoD was not painful to the animals involved. In most cases (63%), the animals were not exposed to or involved in any painful procedures (USDA Pain Category C). In 23% of the cases, animals were given anesthesia or pain-relieving drugs during procedures that might otherwise have involved pain or distress to the animals (USDA Pain Category D). In 14% of the animals used, anesthetics or analgesics were not used because they would have interfered with the validity of the results of experiments (USDA Pain Category E). Since FY94 the use of animals in Pain Category E has decreased steadily resulting in an overall decrease of 54% (59,808) (Figure IV-18). A majority (91%) of the animals used in painful experiments (where reducing the pain or distress would have interfered with the validity of the results) were rodents. Fish accounted for 8% of the animals in USDA Pain Category E and other mammals accounted for less than 1% of animals in this pain category. Eighty-nine percent of the animals reported in USDA Pain Category E were used in medical studies; of these, 60% of the animals were used in research on infectious disease and chemical and biological defense and 18% in ionizing radiation studies. Infectious disease and chemical and biological defense research falls into USDA Pain Category E because the animals have to be exposed to chemical or biological agents or antidotes or other infectious diseases or vaccines, which may result in some type of distress. There were no animals subjected to unalleviated pain during training studies.

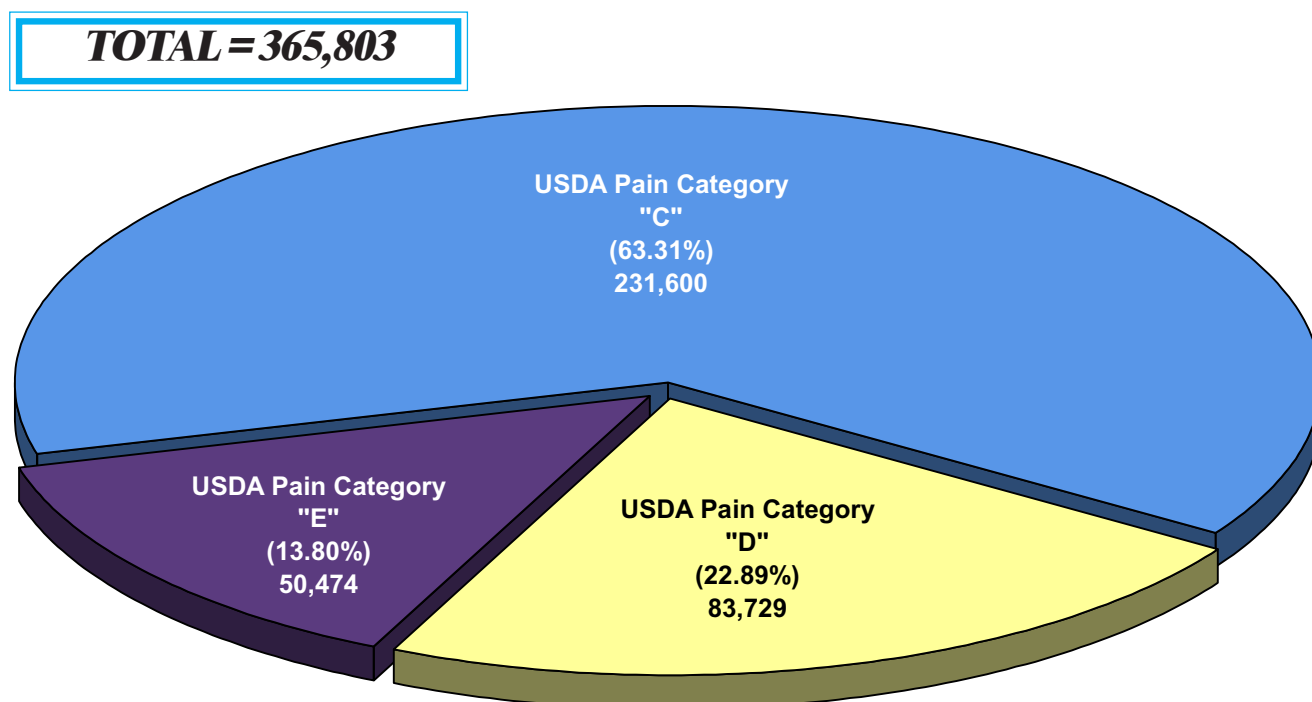


Figure IV-15 DoD Intramural and Extramural Animal Use by USDA Pain Category for FY00

Percentages may not add up to 100% due to rounding of calculations

TOTAL = 187,234

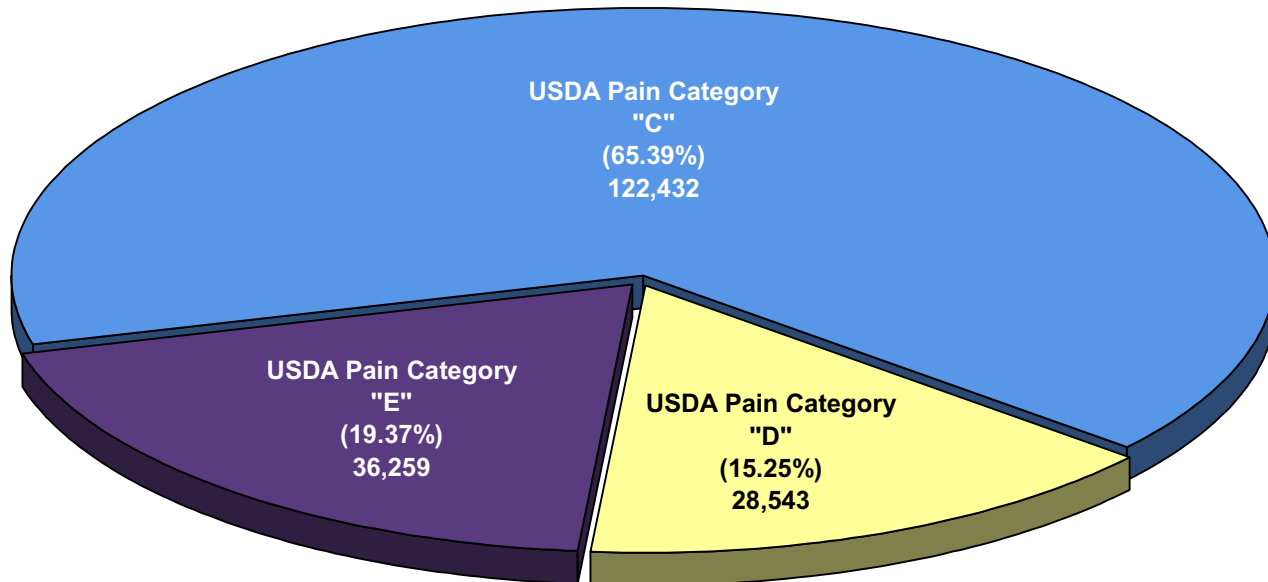


Figure IV-16 DoD Intramural Animal Use by USDA Pain Category for FY00

Percentages may not add up to 100% due to rounding of calculations

TOTAL = 178,569

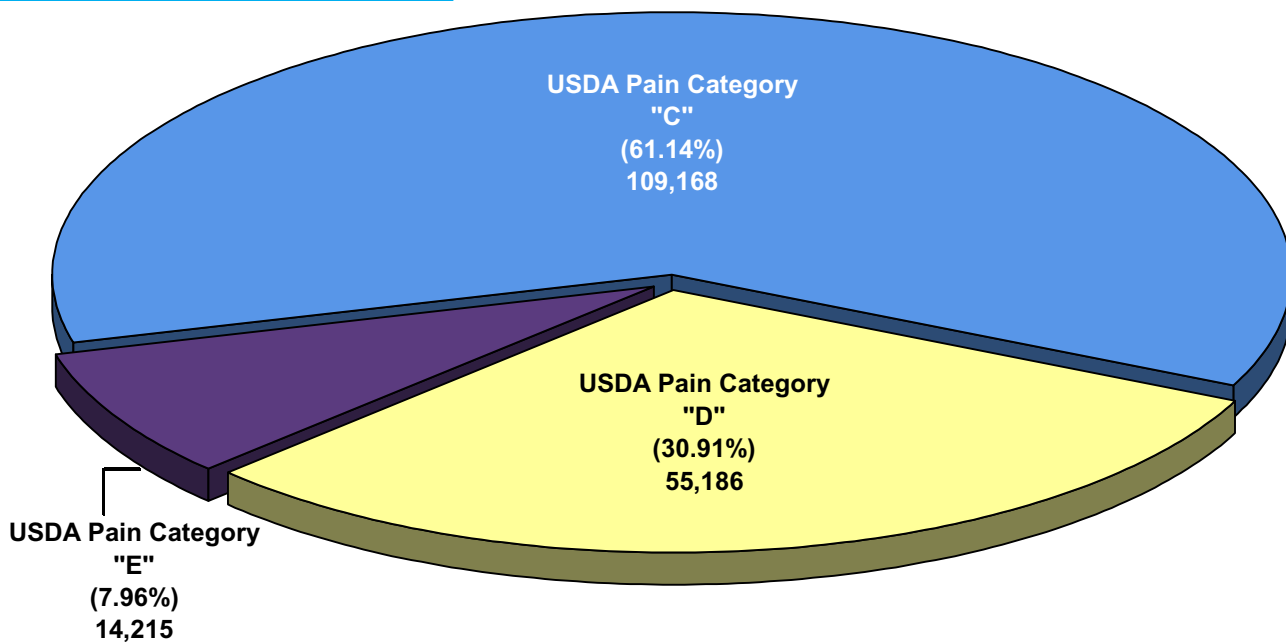


Figure IV-17 DoD Extramural Animal Use by USDA Pain Category for FY00

Percentages may not add up to 100% due to rounding of calculations

The DoD clearly has a most diverse, unique, and demanding research and development mission. The modern battlefield is a hostile and dangerous environment with extraordinary potential for exposure to lethal or debilitating conventional weapons, exotic endemic diseases, biological and chemical agents, nuclear blast and radiation, directed energy sources, and complex and dangerous equipment. In addition, a host of adverse environmental conditions, such as cold, heat, high and low pressure, and G-forces are threats to service men and women. The DoD must provide acceptable protection against these threats and many others. The animals reported in USDA Pain Category E were used in research designed to find ways to protect service men and women from the threats they encounter daily. Note that in many of these Pain E studies the distress level is minor, such as in heat stress or gastrointestinal distress after being exposed to G-forces. This critical research is often reliant upon animal models for vaccine and efficacious countermeasure development.

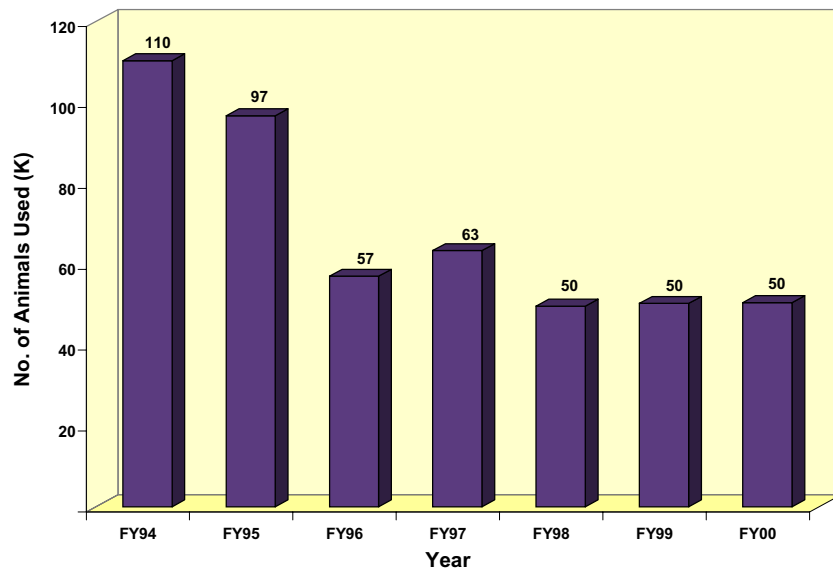


Figure IV-18 USDA Pain Category E for FY00

SECTION V

DoD INITIATIVES TO PROMOTE ALTERNATIVE METHODS THAT REPLACE, REDUCE, AND REFINE THE USE OF ANIMALS

Alternatives, as articulated in *The Principles of Humane Experimental Technique* (Russell and Burch, 1959), are defined as methods that Replace, Reduce, and Refine the use of animals. In addition to these Three Rs, the Department of Defense (DoD) advocates a fourth R, “Responsibility,” for implementing these alternative methods.

Replacement

The replacement alternative addresses supplanting animal use with nonliving systems, analytical assays, cell-culture systems, and with animals that are lower on the phylogenetic scale.

Reduction

Decreasing the number of animals used through the use of statistical or innovative design strategies, while preserving the scientific integrity of the biological model, is a major emphasis of the reduction alternative to animal use.

Refinement

Procedures or measures taken to eliminate or minimize pain or distress in the animal(s) or enhance well-being. Examples of refinement include but are not limited to the use of analgesia to decrease pain or distress, the use of remote telemetry, which decreases the distress of restraint, or the use of adjusted early experimental endpoints.

Responsibility

The DoD has taken responsibility for implementing animal use alternatives. This commitment illustrates the DoD’s initiative toward utilization and development of alternatives to animal use.

Department policy with regard to animal alternatives is promulgated in DoD Directive 3216.1, which directs that “it is DoD policy that alternatives to animal species should be used if they produce scientifically satisfactory results.” This policy is implemented in the Joint Regulation on the Use of Animals in DoD Programs, which delegates responsibility to the local commander for utilization of alternatives to animals.

To illustrate the Department’s initiatives to promote these Four Rs, a description of such initiatives within DoD’s research laboratories and medical treatment centers is provided. The lists included in this section are not all inclusive, as the number of specific examples of implementing alternative methods that can be documented for DoD’s research projects is extensive. Rather, it illustrates the scope, diversity, and spirit of DoD’s Four Rs initiatives. This section will demonstrate a broad-based movement toward the use of biotechnology and other innovative adjuncts to replace and reduce animal use as well as refinement in methods used in essential animal studies.

V.1 DoD INITIATIVES TO PROMOTE ANIMAL ALTERNATIVES

The DoD has established a variety of initiatives and targeted programs that are currently in place to promote alternative methods that will replace, reduce, and refine the use of animals. These programs are designed to target individual and institutional awareness by providing educational opportunities, professional training, and fiscal resources toward implementing the Four Rs approach to animal use.

V.1.1 Science and Technology Objectives to Reduce Reliance on Animal Research

The DoD continues to seek alternatives to animal use through a research objective initiated in FY93 and continuing through FY04 entitled “Reducing Reliance on Human and Animal Subjects of Research and Improving Experimental Conditions Using Animals.” The objectives of the STEP are to conduct basic research to develop new technologies to incrementally reduce future reliance on research animals. The U.S. Army Medical Research and Materiel Command’s Medical Biological Defense Research Program budgeted approximately \$368,000 in FY00 for this objective, which is available to support alternatives to animal use in research.

V.1.2 DoD-Sponsored Conferences and Workshops on Alternatives to Animal Use

Since 1990 the DoD has been promoting responsibility for alternatives to animal use by sponsoring major meetings and conferences on the subject. Every 2 years the DoD sponsors an international meeting on Alternatives to Animal Testing (Table V-1). These biennial conferences have been sponsored by the U.S. Army Soldier and Biological Chemical Command (SBCCOM) and such prestigious cosponsors as the National Institute of Environmental Health Sciences (NIEHS), the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD), the U.S. Army Center for Health Promotion and Preventive Medicine (CHPPM), the U.S. Navy, the U.S. Air Force, Xenogen Corporation, the Gillette Company, the Humane Society of the United States, DermTech International, Interagency Committee on Neurotoxicology, Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the National Capital Area Chapter - Society of Toxicology, and the Association of Government Toxicologists.

The 1992 meeting had 35 scientific platform sessions and 22 scientific poster presentations. This international symposium was attended by nearly 300 military and civilian scientists from four countries. Proceedings of the 1992 symposium are available through the Defense Technical Information Center (DTIC). In addition, in 1994 a book edited by Dr. Harry Salem entitled *Animal Test Alternatives* was published by Marcel Dekker, Inc., which included chapters prepared by most of the presenters at this symposium.

The 1994 meeting had 26 scientific platform sessions, including one by Dr. Martin Stephens of the Humane Society of the United States, and 45 scientific poster presentations. This meeting was attended by over 330 military and civilian scientists from seven countries. The proceedings and a monograph based on this successful symposium are available through DTIC. *Advances in Animal Alternatives for Safety and Efficacy Testing* was published by Taylor and Francis.

The 1996 conference was coordinated with the Scientists Center for Animal Welfare, which held its meeting June 10-11, 1996 to present Animal Welfare and Toxicology/Safety Studies: Current Issues and Trends for the Next Century. In December 1998, the Alternative Toxicological Methods for the 21st Century: Protecting the Human Health and Advancing Animal Welfare conference was held in Bethesda, Maryland. This conference was sponsored by the SBCCOM, the CHPPM, the USAMRICD, and the

Table V-1. DoD-Sponsored Conferences

1990	DoD Initiatives in Alternatives to Animal Testing
1992	Current Concepts and Approaches on Animal Test Alternatives
24-26 May 1994	Alternatives in the Assessment of Toxicity: Theory and Practice
12-14 June 1996	Biennial International Symposium on Alternatives in the Assessment of Toxicity Issues, Progress and Opportunities
December 1998	Alternative Toxicological Methods for the 21 st Century: Protecting the Human Health and Advancing Animal Welfare
November 2000	Alternative Toxicology Methods for the New Millennium—Science and Application

NIEHS. The purpose of this conference was to present the latest research and trends in programs to replace, reduce, or refine the use of research animals.

The 6th Biennial Alternatives Symposium entitled *Alternative Toxicology Methods for the New Millennium - Science & Application*, was held in late November 2000 at the Lister Hill Center at the National Library of Medicine in Bethesda, Maryland. It provided 3½ days of cutting edge scientific presentations and over 30 poster presentations. Papers were presented by researchers from SBCCOM, USAMRICD, CHPPM, Edgewood Chemical Biological Center, Defense Advanced Research Projects Agency, U.S. Navy, U.S. Air Force, Yale, Harvard, Johns Hopkins, Massachusetts Institute of Technology, University of Michigan, Food and Drug Administration, and the Environmental Protection Agency.

V.1.3 National Research Council, Institute of Laboratory Animal Research, Educational Programs

The Department's priority and continuing commitment to promoting individual and institutional responsibility for alternatives to animal use are reflected in continuing financial support of the Institute of Laboratory Animal Research (ILAR) educational program of the National Research Council. The principal thrust of the ILAR grant is development of institutional training materials, educational courses, and publications in support of the Department's laboratory animal care and use programs. This ILAR information is used in various military research facilities as an important adjunct to existing investigator training and technical education programs on animal care and use. The ILAR information and programs have generated strong animal alternative provisions for both civilian and military-specific research opportunities. The Department has funded this work since 1987 through 5-year grants and is currently providing funding under the third such grant. Even in the face of diminishing research funds, the Department has resolved to maintain this important collaboration by providing in excess of \$130,000 annually for the ILAR program.

V.1.4 Institutional Animal Care and Use Committee Emphasis

Title 9 (Animals and Animal Products), Subchapter A (Animal Welfare), Parts 1-4 of the *Code of Federal Regulations* has specific provisions for addressing the issue of alternatives during the research animal protocol review process. The DoD has been a leader in constituting and operating Institutional Animal Care and Use Committees (IACUCs) at its biomedical research facilities. Accordingly, DoD IACUCs consider alternatives to the proposed use of animals as an important review consideration. All DoD programs use a standardized IACUC protocol format (Appendix C) for animal use proposals, which requires that nonanimal alternatives be considered. It states, "No study using animals should be considered prior to the elimination of all reasonable possibilities that the question might be adequately answered using other than animal means." Investigators must provide information on the animal model being proposed and justification for the selected species. The instructions for the standard protocol format states, "investigators should use the least sentient species that will permit the attainment of research objectives." In addition, the investigators are required to provide a short description of the features of the proposal that may qualify the study as one that replaces, reduces, or refines the use of animals. The DoD 1995 Policy Memorandum (Appendix B) requires that extramural contractor proposals utilizing animals in research, education, testing, or training include all the information contained in the DoD standard protocol format, thereby requiring them to also provide the alternatives information.

V.2 DoD PARTICIPATION IN OTHER FEDERAL ANIMAL ALTERNATIVE PROGRAMS

The National Institutes of Health Revitalization Act of 1993 (Public Law No. 103-43, Section 1301) directed the NIEHS of the National Institutes of Health to establish an Applied Toxicological Research and Testing Program, which represents the NIEHS' component of the National Toxicology Program. The Act further directed the NIEHS to "(a) establish criteria for the validation and regulatory acceptance of alternative testing methods, and (b) recommend a process through which scientifically validated alternative methods can be accepted for regulatory use." To fulfill this mandate, an ad hoc ICCVAM was established in 1994 by NIEHS. In 2000, P.L.106-545, the ICCVAM Authorization

Act of 2000, established ICCVAM as a permanent committee. The mission of ICCVAM is to coordinate issues throughout the Federal government that relate to the development, validation, acceptance, and harmonization of toxicological test methods. The ICCVAM is responsible for the coordination of the development and review of various alternative toxicological methods. The ICCVAM must also facilitate communication among all stakeholders in the development and review process of alternative methods. The ICCVAM evaluates proposals for alternative test methods and recommends further research. The ICCVAM comprises 38 members representing 15 different U.S. Federal agencies. Members serve as points of contact and as sources to identify technical experts from their agencies to serve on specific topical workgroups. The recommendations regarding the usefulness of test methods provided by ICCVAM enable U.S. Federal agencies to assess risks entailed by various test methods and make regulatory decisions. In FY00 the DoD had three representatives on the ICCVAM from U.S. Army Edgewood Research Center, the U.S. Army Center for Environmental Health Development Laboratory, and the U.S. Air Force DoD Tri-Service Toxicology Laboratory. The ICCVAM determines what assays warrant peer review, from working groups, and support test method workshops. When the members of the ICCVAM agree that an alternative method merits investigation, a working group is assembled. The working group in turn determines whether sufficient information exists for the assembly of either a peer review or a test method workshop. During FY00, there were three different working groups organized by the ICCVAM and the DoD had representatives on two of the three working groups - the Corrosivity Working Group, which evaluated the Corrositex(r) assay and the Developmental Toxicology Working Group that evaluated Frog Embryo Teratogenesis Assay - Xenopus. The results generated by ICCVAM's working groups may be used to recommend U.S. Federal regulations and/or guidelines for research. More information on ICCVAM can be found at <http://iccvam.niehs.nih.gov/>.

Presentations have also been made on alternatives to the Board of Scientific Counselors of the National Toxicology Program of the National Institute of Environmental Health Sciences, Board of Scientific Counselors of the Food and Drug Administration, and Cancer Etiology Group at the National Cancer Institute.

V.3 DoD EXPERTISE AND TRAINING PROGRAMS THAT PROMOTE ANIMAL ALTERNATIVES

V.3.1 Veterinary Staff Expertise and Assistance Visits

The DoD component oversight offices each have credentialed laboratory animal medicine (LAM) veterinarians serving in key staff positions. In addition to being advisors to commanders on issues related to animal welfare and alternatives to animal use, these veterinarians provide oversight and structure to the command's animal care and use programs. These officers also make periodic staff assistance visits to subordinate facilities that use animals and evaluate each laboratory animal care and use program. Consideration of the use of alternatives is reviewed on these staff assistance visits. Another important responsibility of the LAM veterinarian is to review extramural animal use protocols, ensuring that alternatives to animal use and personnel training issues have been addressed.

V.3.2 Professional Veterinary Training in LAM

The individuals who are specialty trained in veterinary LAM provide expertise in DoD biomedical research institutions, which strongly correlates to effective animal use alternatives programs. In FY00, 33 board-certified specialists of the American College of Laboratory Animal Medicine (ACLAM) served in the DoD. The DoD has long been a leader in training veterinarians in the field of LAM, the biomedical and veterinary specialty most closely associated with laboratory animal welfare and laboratory animal care and use programs. Many of the nationally prominent leaders of several laboratory animal associations were formally trained in, or closely associated with, DoD LAM training programs. Examples are the current President of the American Association for Laboratory Animal Science (AALAS), the president elect of the American Society of Laboratory Animal Practitioners (ASLAP), the current Secretary-Treasurer of ASLAP and ACLAM, and several past presidents of ACLAM. This traditional DoD strength in LAM expertise strongly enhances both animal care and use and animal alternatives programs. Of the ACLAM members, many have received some or all of their LAM training in DoD LAM training programs.

V.3.3 AALAS Technician and Laboratory Animal Science Training

There are a number of DoD research facilities that sponsor formal training programs leading to certification of animal care and research personnel as AALAS laboratory animal technicians. This specialized training is offered to both government technicians and non-government contractors. It is an important mechanism for ensuring highly qualified animal care and research technicians in Defense laboratories. Individual DoD institutions have sponsored formal seminars for research personnel where experts from the National Agricultural Workshop present formal training and information on alternatives to animal use. In addition, the Walter Reed Army Institute of Research (WRAIR) offers quarterly a workshop on ethical and administrative issues relating to animal use. The AALAS technicians' course curriculum and the WRAIR workshop curriculum include formal training and information on alternatives to animal use.

V.4 DoD IMPLEMENTATION OF ANIMAL USE ALTERNATIVES

DoD research protocols strive to minimize the number of animals used to accomplish the program's mission and goals. During the review of protocols by the IACUC, investigators are specifically asked to present information indicating that "Reduction, Replacement, and Refinement" have been addressed in the animal study. Implementation of these alternatives reduces, replaces, and refines the Department's use of animals in research. This is accomplished by the implementation of both general and specific alternatives. In addition to the implementation of alternatives, the DoD has established policies specific to the refinement of animal use. For example, WRAIR has established a policy that mandates consideration of environmental enrichment for research animals. This policy allows for flexibility and creativity for improving conditions of laboratory animals.

General alternatives are those that are frequently implemented in many different DoD programs. In FY00, 35 intramural institutions reported over 750 general animal use alternatives that they were implementing. Six institutions with 52 projects reported eliminating the use of animals by the implementation of alternative methods. Ninety-eight projects from 20 institutions reported using nonanimal training aids to reduce the number of animals required for training.

V.4.1 General Alternatives Implemented in FY00

The following examples are a representative listing of general alternative methods commonly practiced in DoD facilities:

Replacement

- During the review process, all potential methods of adequately answering the research objective are reviewed prior to the use of an animal model.
- The evaluation process also considers the selection of a particular animal type; species lower on the phylogenetic scale are considered and used if their selection permits attainment of the research objectives.
- Nonanimal training aids are used to replace the use of live animals.
- Computer simulations are used to replace live animals when scientifically possible.

Reduction

- Animal use protocols are subject to review by a biostatistician who addresses the animal used, study design, and statistical evaluation packages, and ensures that the minimum number of animals will be used to meet the specific scientific objectives.

- Pilot studies are used to refine techniques and define the animal model so that animal use can be kept to the minimum required for statistical significance.
- Sharing of animal tissues with other investigators reduces animal use.
- Iterations of the experiments are combined when possible to reduce the number of control animals used.
- Collaboration between DoD investigators allows for a single animal to be used in multiple training and research procedures and the sharing of control group information, resulting in an overall reduction in the number of animals used.
- Several types of data are collected simultaneously.
- Training sessions are designed to use the highest practical student-to-animal ratio.
- When possible, animals serve as their own controls.
- Studies are deliberately phased so they continue to progress only if warranted.

Refinement

- Parameters developed for early or alternative endpoints are used as experimental endpoints when possible.
- Animals are anesthetized before euthanasia to decrease stress.
- Moribund animals are humanely euthanized to prevent unnecessary pain or distress.
- Utilizing the environmental enrichment strategy, animals are housed in social settings (i.e., pairs or groups) in an enriched environment (e.g., nestboxes and toys).
- Animal-handling skills and clinical techniques are taught to animal technicians, investigators, and research assistants to increase or ensure a proper skill level is attained prior to the start of a protocol.
- All Advanced Trauma Life Support training laboratory procedures are performed while the animals are under general anesthesia, and they are euthanized without regaining consciousness.

V.4.2 Specific Alternatives Implemented in FY00

Specific alternatives are those that may be specific to both a research protocol and/or facility. In FY00, 35 institutions reported implementing over 140 specific alternatives. Specific alternatives implemented by the DoD in FY00 were categorized as a subset of replacement, reduction, or refinement and are shown in Table V-2. These categories illustrate the broad-based spectrum of alternatives to be implemented by the DoD. A representative listing of the specific alternatives by alternative type and research category is presented in Appendix P.

V.5 DoD DEVELOPMENT OF ANIMAL USE ALTERNATIVES

A review of the FY00 DoD research reveals that DoD organizations were actively involved in the development of alternatives to animal use. These developments occur through research specifically designed to produce alternatives and to improve experimental techniques. Whenever possible, DoD investigators attempt to develop state-of-the-art, scientifically relevant, and reliable experimental procedures that can be performed without the use of animals. In addition, in cases where the animal models cannot be completely replaced, investigators and veterinary staffs work diligently to develop refinement techniques to minimize animal pain and distress and improve the quality and quantity of data through the use of technology. The DoD is very active in the development of alternatives to the use of animals in research. Below are examples of alternatives developed that the DoD reported to be completed in FY00. This is only a sample of the alternatives development that was completed this year.

V.5.1 Sample Alternatives Development Completed During FY00

Replacement

Replacement Using *in vitro* Cell Cultures:

- Developed systems to harvest osteoclasts from euthanized porcine bone marrow rather than from live mouse pups.
- Developed systems to harvest articular and meniscus cartilage from euthanized porcine carcasses from training labs for molecular phenotyping work.
- Developed cultured human eye cells to evaluate the effects of laser injury and therapeutic approaches.
- Developed a system to produce monoclonal antibodies to ricin via hybridomas *in vitro* instead of inducing ascites tumors in mice.
- Established procedure to use bovine teeth and incisors from slaughterhouse carcasses in the study of the antimicrobial activity of calcium hydroxide and chlorhexidine gluconate.

Replacement Using Non-mammalian Species or Species Lower on the Phylogenetic Scale:

- In the assessment of protection of botulinum neurotoxin fragments against intoxication with botulinum, mice have replaced the use of nonhuman primates (NHPs).
- The use of guinea pigs to study Ebola virus pathogenesis reduces the number of NHP studies needed to gain full understanding of Ebola infection in man.

Biochemical/Physical Methods:

- In studies of cytotoxic T lymphocyte responses to alphavirus replicons expressing filovirus proteins, cloned cells are used instead of mice.
- *In vitro* cell culture assays specific to RNA challenge, viruses are used as part of the overall evaluation of the viruses in question.

Reduction

Biochemical/Physical Methods:

- In staphylococcal enterotoxin B research, extensive *in vitro* assays are conducted; thus, fewer rhesus monkeys are required to demonstrate efficacy of our candidate vaccine.
- Developed *in vitro* assays that significantly increased the detection of protein expression, resulting in the use of fewer mice.

Substitution of Computer Simulation, Models, or Other Technologies:

- In the characterization of recombinant bacterial superantigen vaccines, the use of computer modeling and *in vitro* testing decreases the number of mice required.
- Development of efficient methods for the monitoring of cartilage softening in rabbit ears that yield minimal tissue destruction and require fewer animals.

Refinement

Reduce Pain and Distress:

- Propagation of the Leishmania organism in the tail of the gerbil greatly reduces the apparent distress experienced by the subject.
- Individual minute volume measurements will be carried out on each rabbit prior to aerosol challenge to refine the dose they receive, resulting in use of fewer animals to achieve statistically significant results.
- Use of fewer sarcoma cells per mouse decreases the likelihood of solid tumor production in adult mice, thus the amount of distress in these animals.

V.5.2 Sample Alternatives Undergoing Development During FY00

As an ongoing process, the DoD is continuously developing alternatives. Below are examples of alternatives that were reported as currently in development by the DoD during FY00. This is only a sample of the alternatives being developed this year.

Replacement

Biochemical/Physical Methods:

- Gene and protein expression resulting from laser exposure is being explored in studies on the risk assessment of the eye and safe laser wavelength for cornea and skin.
- An artificial eye was developed that mimics the focusing characteristics of the real eye. Experiments are being conducted to determine the nonlinear optical properties of the eye with and without an artificial retina, dramatically reducing the number of animal subjects needed to delineate retinal damage mechanisms for ultrashort retinal damage.
- The Multiplex Photonic/Electronic Sensor for biological warfare agents is being developed to detect known and potential biological warfare agents without the use of animals to determine their pathogenicity, therefore, reducing the number of animals needed to determine the probable pathogenicity of an agent. It has resulted so far in a growth medium that distinguishes anthrax from other related nonpathogenic bacteria and methods to recognize pathogenic proteins and genes related to their production.

Replacement with Computer Simulation, Models, or Other Technologies:

- Computer models for target detection to replace dolphins are being developed.
- Sonar and signal processing methods to replace marine mammals are in development.
- In order to understand the possible health consequences of exposure to variety of military and civilian electronic devices, scientists must know how the electromagnetic pulses move through the head and where, within the head, the pulse deposits its energy. Research is being performed on the computation of pulse propagation through living organisms. Computing this propagation will reduce or eliminate the need to measure the propagation in animals, except possibly for confirmatory reasons.
- Validation of computer modeling efforts to predict microwave energy absorption in the laboratory rats is under way.

Replacement Using *in vitro* Cell Cultures:

- Monoclonal antibody bioreactor is undergoing validation studies to replace the use of mice in infectious disease studies.

- In studies on pathogenic mechanisms of nonfreezing cold injury, cell tissue culture systems will be utilized to assess presence or absence of specific receptor systems and thereby possibly eliminate potential needless use of animals in protocols using irrelevant receptor antagonists.
- Testing of the mechanism of action and efficacy of a putative new anticonvulsant, neuropeptide-Y using neuronal cultures, which will diminish the number of rats and eliminate the pain factor of intracerebroventricular injections.
- Research on the mechanisms of high power microwave radiofrequency radiation (RFR) bioeffects in living cells is being performed so that similar studies in living animals can be more focused and thereby reduce the number of animals needed. It has resulted in the application of Quantitative Luminescence Imaging System to pulsed RFR in order to predict bioeffects and ways to assess tissue level absorption of RFR without using laboratory animals.

Non-Mammalian Species or Species Lower on the Phylogenetic Scale:

- In studies on effects of neurotoxicologic compounds in aquatic toxicity test species, the startle response of the bluegill sunfish is being investigated as an alternative to conventional neurotoxicologic tests that use laboratory rats.
- Uptake of bromodichloromethane (BDCM), a disinfection by-product, by the medaka lays the groundwork for physiologically based pharmacokinetic modeling. Further studies use diethylnitrosamine and BDCM to explore cancer occurrence and its relation to rapidly dividing liver cells in the medaka. Results will be compared with similar data for conventional laboratory animals.
- Determination of the efficacy and immune response of two lots of anthrax vaccine preparation in the rabbit model of inhalational anthrax.
- Development of the adult frog model to support the reproductive toxicity program.
- Development of a murine model for the assessment of neuropathogenicity of NHP herpes viruses.
- Development of a miniature pig model to replace the rhesus monkey retinal model used in retinal research.

Reduction

Substitution of Computer Simulation, Models, or Other Technologies:

- The predictive toxicology program is developing innovative toxicity testing methodologies focused on *in vitro* and computational modeling approaches to accurately predict the human health risks of new Air Force systems, materials, and technologies, that will reduce the number of animals required.
- Virtual models and robotic trauma manikins that will replace the use of goats in Advanced Trauma Life Support Course Practicum are being developed.
- Development of computer mathematical finite difference time domain calculations to predict the amount of energy absorbed by the NHP. Similar code is being developed for human dosimetry predictions and is validated by the NHP computer models.
- Development of a physiologically based pharmacokinetic model for ammonium perchlorate will reduce the number of animals required for studying this compound.

Utilization of Alternative Biological Testing Methods:

- Based on information from the Human Genome Project, the Army has used gene expression microarray technology to evaluate damage and repair processes after laser injuries. Molecular and computer methods from such areas as genomics, proteomics, and bioinformatics have been applied to evaluate the cellular responses from several hundred up to 18,000+ known genes. This will eliminate the use of animals in making the first stage assessment regarding therapeutic efficacy and reduce the total number of animals required to confirm *in vivo* therapy effects.

- The tissue culture model of seizures allows the screening and the description of the effects of a large number of neuropeptide transmitter agonists and antagonists using the minimum number of rats.
- In research on advanced vaccines against the causative agent of scrub typhus, scientists are developing high titer inoculum in mice; therefore, the amount of inoculum needed for each challenge experiment is reduced, which may reduce the need to make additional inoculum in mice.
- To reduce the numbers of animals needed to test malaria vaccine constructs, all plasmids are first tested *in vitro* for expression of the protein product.
- Knowledge of the optimal doses for the plasmids in previous experiments reduces the number of animals required to test the Good Manufacturing Practice lots.
- In testing malaria vaccines in NHPs, the highest doses of each antigen will be tested first; if no response is seen, lower doses will not be tested.
- To reduce the numbers of mice for testing malaria vaccines, all immunization studies, 3-4 synthetic peptides or DNA plasmids, will be evaluated at the same time.

Refinement

Environmental Enrichment:

- Development of environmental enrichment for NHP by engaging them in behavioral interaction that emulates the essential features of natural foraging. The results will be used to further refine the environmental condition of captive NHP and ensure their psychological well-being.
- Novel strategies and methods for improved environmental enrichment are being evaluated for many different animals.

Increased Training for Research Personnel to Improve Skills:

- Development of training programs to teach research personnel the technical skills necessary to properly manage and humanely handle NHP during research experiments.
- Instruction in the care, handling, and management of rodents and lagomorphs.
- Development of veterinary techniques training programs for personnel utilizing various laboratory animal species will result in better animal handling.
- Training in surgical and aseptic techniques results in shorter surgery duration, less tissue trauma, and decreased post-operative complications.

Reduce Pain and Distress:

- CT scanning will be used to monitor the progress of the disease in animals with minimal invasive procedures to significantly reduce stress.
- In preparation of immune sera in rabbits for use in specific identification of *Burkholderia mallei*, in each preparation, Ribi Adjuvant System will be used initially and if adequate titer is obtained, Freund's adjuvant will not be used, thus minimizing the risk of potential pain or distress.
- Development of a nonsurgical animal model for enterotoxigenic *E. coli* Diarrhea Disease will replace the removable intestinal tie, adult rabbit diarrhea (RITARD) surgical animal model and provide a major refinement over the RITARD model.
- Development of polyclonal antiserum against anthrax toxin components will serve as a potential replacement for Freund's adjuvant system with equally effective, but less reactive, adjuvant.
- Determination of a surrogate marker to predict death instead of going to death as an endpoint will reduce unnecessary stress.
- Assessment of anesthetic risks and protocol development in chinchillas avoids overdosing in experimental research protocols.

Table V-2. Specific Alternatives CategoriesReplacement

- Non-mammalian species or species lower in the phylogenetic scale
- Biochemical/physical methods
- Computer simulations
- Other species replace companion animals
- Replacement using *in vitro* cell cultures
- Substitution of another species

Reduction

- Utilization of alternative biological testing method
- Substitution of computer simulations or other technologies
- Enhanced protocol design

Refinement

- Reduce pain
- Reduce distress
- Research models and animal alternatives

V.6 SUMMARY

Each year new techniques and capabilities improve the handling, treatment, and use of animals in RDT&E and training and potentially reduce the need for animals in those same endeavors. In FY00, there was significant evidence of the DoD's aggressive pursuit to develop alternatives to replace, reduce, and refine the use of animals (examples are highlighted in Section V.5). In addition to these developmental efforts, animal use data for FY00 indicate the widespread implementation of validated alternatives. Fish are now replacing the use of mice and rats while rats and mice continue to replace NHP and other mammals higher on the phylogenetic scale in vaccine and drug development efforts. These and other examples of the development and implementation of alternatives have translated into reductions in the overall use of animals higher on the phylogenetic scale (see Section V.5). Animal use alternatives including reduction, replacement, and refinement constitute key initiatives in the biomedical RDT&E, and educational training programs of the DoD. The number of large animals used by the military departments over the past decade has been significantly reduced, and some large species are rarely used at all. Dogs, cats, NHP, and marine mammals collectively have decreased 19% from FY94 - FY00 and represent less than 1% of the total animals used in research by the DoD.

SECTION VI

GLOSSARY

Adjuvant: An agent mixed in a vaccine to enhance the immunological protection afforded.

Alternatives to Animal Use: For purposes of this assessment, “alternatives” are defined as encompassing any subjects, protocols, or technologies that replace the use of laboratory animals altogether; reduce the number of animals required; or refine existing procedures or techniques so as to minimize the level of pain and distress endured by the animal. These technologies involve the continued, but modified, use of animals; use of living systems; use of chemical and physical systems; and use of computers.

Analgesic: An agent that relieves pain without causing loss of consciousness.

Anesthetic: An agent that causes loss of the sensation of pain. Anesthetics may be classified as topical, local, or general.

Animal: For purposes of this assessment excluding embryos, animal is defined as any nonhuman member of five classes of vertebrates: mammals, birds, reptiles, amphibians, and fish. Within this group, two kinds of animals can be distinguished, warm-blooded animals (mammals and birds) and cold-blooded animals (reptiles, amphibians, and fish). Under this definition, invertebrates are not included.

Animal Use: As any whole nonhuman vertebrate, living or dead, excluding embryos, that was used for research, development, test, and evaluation (RDT&E), clinical investigations, diagnostic procedures, and/or instructional programs. Only live animals or whole dead animals, as defined, that were either on hand in the facility or acquired and used during FY00 are included. Animal organs, tissues, cells, blood, fluid components, and/or byproducts purchased or acquired as such animal/biological components are not reported. This definition does not include animals used or intended for use as food for consumption by humans or animals, animals used for ceremonial purposes, or military working animals and their training programs.

Animal Welfare Act: This act, passed in 1966 and amended in 1970, 1976, 1985, and 1990, was originally an endeavor to stop traffic in stolen animals that were being shipped across state lines and sold to research laboratories. Amendments to the act have expanded its scope to include housing, feeding, transportation, and other aspects of animal care.

Antibody: Proactive proteins produced by lymphocytes (a type of white blood cell) that can specifically bind foreign substances.

Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC): A voluntary private organization that has provided accreditation for over 600 institutions. AAALAC accreditation is based on program compliance with the provisions of the National Research Council’s (NRC) *Guide for the Care and Use of Laboratory Animals*, and is recognized by the Public Health Service (PHS).

Biological Model: A surrogate or substitute for a process or organ of interest to an investigator. Animals or alternatives can serve as biological models.

Biomedical Research: A branch of research devoted to the understanding of life processes and the application of this knowledge to serve humans and animals. A major user of animals, biomedical research affects human health and the health care industry. It is instrumental in the development of medical products such as drugs and medical devices, and in the development of services such as surgical and diagnostic techniques. Biomedical research covers a broad spectrum of disciplines, such as anatomy, biochemistry, biology, endocrinology, genetics, immunology, nutrition, oncology, and toxicology.

Carcinogen: An agent or process that significantly increases the incidence of abnormal, invasive, or uncontrolled cell growth in a population. Carcinogens fall into three classes: chemicals, viruses, and ionizing radiation. A variety of screening assays have been developed to detect chemical carcinogens, including the *Salmonella*-mediated mutagenesis assay (Ames test), the sister chromatid exchange assay, and traditional laboratory animal toxicity tests.

Cell Culture: Growth in the laboratory of cells isolated from multicellular organisms. Each culture is usually of one type. Cell culture may provide a promising alternative to animal experimentation, for example, in the testing of mutagenicity, and may also become a useful adjunct in repeated-dose toxicity testing.

Computer Simulations: The use of specially devised computer programs to simulate cells, tissues, fluids, organs, and organ systems for research purposes: to develop mathematical models and algorithms for use in toxicity testing, and to simulate experiments traditionally done with animals for educational purposes.

Distress: Usually the production of pain, anxiety, or fear. However, distress can also occur in the absence of pain. For example, an animal struggling in a restraint device may be free from pain but may be in distress. Distress can be eased with tranquilizers.

Guidelines for Animal Care and Use: Various organizations outside the Federal government have adopted their own guidelines – e.g., the American Psychological Association’s *Guidelines for Ethical Conduct in the Care and Use of Animals*, which is comprehensive and has been endorsed by Federation of American Societies for Experimental Biology; the American Physiological Society’s *Guiding Principles in the Care and Use of Animals*; and the American Veterinary Medical Association’s *Animal Welfare Guiding Principles*. For Federal guidelines, see Interagency Research Animal Committee, NRC *Guide for the Care and Use of Laboratory Animals*, and PHS Policy.

Institute of Laboratory Animal Research (ILAR): A component of the National Research Council, ILAR performs periodic surveys on the use of laboratory animals.

Institutional Animal Care and Use Committee (IACUC): An institutional committee that reviews research proposals and oversees housing and routine care of animals. The committee’s membership generally includes the institution’s attending veterinarian, a representative of the institution’s administration, users of research animals, and one or more nonscientist and lay member.

Invertebrate: Any nonplant organism without a spinal column, e.g., worms, insects, and crustaceans. Invertebrates account for 90% of the earth’s nonplant species. For the purposes of this assessment, invertebrates are not considered to be animals.

In vitro: Literally, in glass; pertaining to a biological process or reaction taking place in an artificial environment, usually a laboratory. Human and animal cells, tissues, and organs can be cultured in vitro. In vitro testing may hold some promising alternatives to animal testing, e.g., in testing for eye irritation and mutagenicity.

In vivo: Literally, in the living; pertaining to a biological process or reaction taking place in a living cell or organism.

National Research Council's *Guide for the Care and Use of Laboratory Animals*: Revised in 1996, the Guide details standards for animal care, maintenance, and housing. It is used by many animal research facilities, both within and outside the Federal government. The AAALAC and PHS also use it when assessing research facilities for accreditation.

Organ Culture: The attempt to isolate and maintain animal or human organs in *in vitro* culture. Long-term culture of whole organs is not generally feasible, but they can be sustained in cultures for short periods (hours or days).

Pain: Discomfort resulting from injury or disease. Pain can also be psychosomatic, the product of emotional stress. Pain can be induced by mechanical, thermal, electrical, or chemical stimuli, and it can be relieved by analgesics or anesthetics.

Protocol: The written plan of a scientific experiment or treatment.

Public Health Service *Policy on Humane Care and Use of Laboratory Animals*: Revised in 1986, the Policy applies to PHS-supported activities involving animals [including those of the National Institutes of Health (NIH)]. It continues to rely on the NIH *Guide for the Care and Use of Laboratory Animals* (1996), and uses institutional committees for the assessment of programs and maintenance of records.

Reduction: Decreasing the number of animals used through the use of statistical or innovative design strategies, while preserving the scientific integrity of the biological model, is a major emphasis of the reduction alternative to animal use.

Refinement: The refinement alternative for animal use addresses the need to ensure that the maximum humane use of each animal is obtained through proper protocol design and efficient utilization of animals, or through the modification of the experimental design to reduce the ethical cost associated with the study.

Replacement: The replacement alternative addresses supplanting animal use with nonliving systems, analytical assays, cell-culture systems, and with animals that are lower on the phylogenetic scale.

Research Facility: Under the Animal Welfare Act, any individual, institution, organization, or postsecondary school that uses or intends to use live animals in research, tests, or experiments. Facilities that receive no Federal support for experimental work and that either purchase animals only within their own state or that maintain their own breeding colonies are not considered research facilities under the act.

Testing: Standardized procedures that have been demonstrated to predict certain health effects in humans and animals. Testing involves the frequent repetition of well-defined procedures with measurement of standardized biological endpoints. A given test may be used to evaluate many different substances and use many animals. Testing is used to establish the efficacy, safety, and toxicity of substances and procedures.

Tissue Culture: The maintenance *in vitro* of isolated pieces of a living organism. The various cell types are still arranged as they were in the original organism and their differential functions are intact.

United States Interagency Research Animal Committee (USIRAC): Established in 1983, serves as the focal point for Federal agencies' discussions of issues involving all animal species needed for biomedical research and testing.

Veterinary Medicine: The science and art of prevention, cure and/or alleviation of disease and injury in animals. Veterinary medicine includes the management of animal care and use programs.

SECTION VII

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